Introduction

Despite major advances in monitoring technology and knowledge of fetal and neonatal pathologies, hypoxic-ischemic encephalopathy (HIE) remains a serious condition that causes significant mortality and long-term morbidity. HIE is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia (ie, hypoxia, acidosis). Most often, the exact timing and underlying cause remain unknown.The American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) published guidelines to assist in the diagnosis of severe hypoxic-ischemic encephalopathy **(American College of Obstetricians and Gynecologists, 2014).**

The incidence of perinatal asphyxia is two per 1000 births in developed countries, and 10 times higher in developing countries where there may be limited resources. 15-20% die in the neonatal period, and up to 25% of survivors are left with permanent neurologic deficits (**Odd at el., 2017) .**

Perinatal asphyxia is a lack of blood flow or gas exchange to or from the fetus in the period immediately before, during, or after the birth process. Perinatal asphyxia can result in profound systemic and neurologic sequelae due decreased blood flow and/or oxygen to a fetus or infant during the peripartum period. When placental (prenatal) or pulmonary (immediate post-natal) gas exchange is compromised or ceases altogether, there is partial (hypoxia) or complete (anoxia) lack of oxygen to the vital organs. This results in progressive hypoxemia and hypercapnia. If the hypoxemia is severe enough, the tissues and vital organs (muscle, liver, heart, and ultimately the brain) will develop an oxygen debt. Anaerobic glycolysis and lactic acidosis will

result. Neonatal hypoxic-ischemic encephalopathy refers specifically to the neurologic sequelae of perinatal asphyxia**(Hakobyan et al., 2019)**. Ischemia (lack of sufficient blood flow to all or part of an organ) is both a cause and a result of hypoxia. Hypoxia and acidosis can depress myocardial function, leading to hypotension and ischemia. Ischemia can impair oxygen delivery, causing further compromise, as well as disrupt delivery of substrate and removal of metabolic and respiratory by-products (eg, lactic acid, carbon dioxide) **(Lisa and Lu-Ann, 2008).**

Many children have mild effects from hypoxic ischemic encephalopathy, but some have much more severe damage. It is important for you to know that there is a range of possible outcomes. The likelihood and extent of brain damage is related to the degree of neonatal encephalopathy. Most infants with mild to moderate degrees of encephalopathy develop normally, while infants with severe encephalopathy are more likely to develop long-term neurologic morbidity . Severe MRI abnormalities are usually associated with marked EEG abnormalities and poor outcome. Permanent neurologic sequelae can be mild, such as learning difficulties or attention deficit disorder, or may be severe and disabling, including cerebral palsy, epilepsy, visual impairment and severe cognitive and developmental disorders **(van Handel, 2007).**

Until recently, there were no specific strategies for prevention of brain injury in term infants. Management of an infant who is depressed at birth involves following accepted guidelines such as those published by ILCOR and Neonatal Resuscitation Program. The infant is evaluated for hypothermia, which should ideally commence within 6 h of birth for infants with moderate to severe HIE **(Wyckoff et al., 2015) .** Supportive management of seizures, fluid balance, and hematological and

cardiovascular abnormities is essential in ensuring optimal outcomes. Presence of a multidisciplinary team including pediatric neurologists, cardiologists, and other subspecialties as well as institutional capabilities for long term EEG, MRI, and physical and occupational therapies are a requisite for establishment of a cooling protocol at tertiary institutes **(Papile et al., 2014).**

Several grading systems have been developed to assess neonatal encephalopathy in infants with perinatal asphyxia. The Thompson score, which was derived from the Sarnat and Sarnat grading system, is a simple clinical method based on the neurological examination and assessment of respiration and fontanelle tension. The method is quick to perform, requires no additional training for medical and paramedical personal and requires no equipment. Therefore, it is strongly recommended for use in low-income countries, where sophisticated equipments such as continuous electroencephalogram registration, near-infrared spectroscopy and, or, magnetic resonance imaging are unavailable (**Thompson at el., 1997).** It can be used to identify neonates with neonatal encephalopathy, who would be eligible for neuroprotective treatment **(Horn et al., 2013).**

The score consists of a clinical assessment of nine signs (Tone, Level of consciousness ,Fits, Position, Primitive reflexes, Respiration, Fontanel tension). Each sign is scored from 0 to 3 and the score for each day is totalled. The higher the score the more severely affected the infant. Score 0 is considered normal. The maximum possible score on any one day is 22. Infants with score (1–10) are considered to have mild HIE, (11–14) have moderate HIE and (15–22) are considered to have severe HIE. The score is equally applicable in a ventilated infant. It cannot be applied in a paralysed infant**(Thompson et al., 1997).**

Aim of the work

This study was done to assess the role of serial Thompson score at day 1, 3, 7 of life in predicting the early neonatal outcome in post asphyxiated term neonates.

Hypoxic Ischemic Encephalopathy

Definition

Perinatal asphyxia is defined as an oxygen deprivation that occurs around the time of birth, and may be caused by perinatal events such as maternal or foetal haemorrhage, intermittent or acute umbilical cord compression, uterine rupture or shoulder dystocia, influencing the supply of oxygenated blood to the foetus**(Lawn, 2005).** In most cases, infants successfully recover from hypoxia episodes, however, some patients may develop ischemic encephalopathy (HIE), leading to permanent neurological conditions such as seizure disorders, cerebral palsy, cognitive delays, and motor disabilities. Furthermore, asphyxia and ischemia are responsible for the impairment of different organs and systems (central nervous system 28%, cardiovascular system 25%, kidneys 50%, and lungs 23%) **(Bhatti, 2014).**

Hypoxic ischemic brain injury: It describes brain injury due to exposure to hypoxia and/or ischemia as evidenced by biochemical (such as serum creatine kinase brain bound [CK-BB]), electrophysiologic (EEG), neuroimaging (head ultrasonography) [HUS], magnetic resonance imaging [MRI], computed tomography [CT]), or postmortem abnormalities **(Derganc et al., 2008).**

Perinatal asphyxia is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia. The primary causes of this condition are systemic hypoxemia and/or reduced cerebral blood flow (CBF) **(Perlman, 2004).**

Neonatal encephalopathy is a clinical term used to describe an abnormal neuro-behavioral state that consists of a decreased level of consciousness with abnormalities in neuromotor tone. It characteristically begins with the first postnatal day and may be associated with seizure like activity, hypoventilation or apnea, decreased primitive reflexes and the appearance of brain stem reflexes. It doesn't imply a specific etiology, nor does it imply irreversible brain injury **(Synder and Cloherty, 2004).**

Epidemiology

The incidence of HIE is reportedly high in countries with limited resources; however, precise figures are not available. It is one of the top 20 leading causes of burden of disease in all age groups (in terms of disability life adjusted years) by the World Health Organization and is the fifth largest cause of death of children younger than 5 years (8%). Although data are limited, birth asphyxia is estimated to account for 920,000 neonatal deaths every year and is associated with another 1.1 million intrapartum stillbirths. More than a million children who survive birth asphyxia develop problems such as cerebral palsy, mental retardation, learning difficulties, and other disabilities **(Lawn et al., 2005).**

In Egypt: Hypoxic-Ischemic Encephalopathy is not an un-common health problem in Egypt. It tops the list for morbidity because of its significant health and social burden **(El Metwally, 2006).** A study from Children's Hospital, Cairo University showed that hypoxic ischemic encephalopathy cases represented 12.2% of the admissions to the NICU and were responsible for 18.8% of deaths **(Seoud et al., 2005)**

Twenty to twenty five % of infants with HIE die in neonatal period and 25 to 30 % of survivors are left with permanent neurodevelopmental

abnormalities as cerebral palsy (CP) or mental retardation **(stoll and kliegman, 2008).**

According to synder and Aurora (2004), incidence of perinatal asphyxia is about 1 to 1.5% in most centers and is inversely related to gestational age and birth weight. It occurs in 9% of infants less than 36 weeks gestational age and in 0.5% of infants more than 36 weeks gestational age. The incidence is higher in term infants of diabetic or toxemic mothers. In both preterm and term infants, intrauterine growth retardation and breech presentation are associated with.

RISK FACTORS

A variety of maternal, obstetric, and neonatal conditions predispose the fetus and newborn to asphyxia. These risk factors are associated with reduced blood flow and/or oxygenation directed to the tissues.

▪ **Antepartum conditions:**

- Abnormal maternal oxygenation (eg, severe anemia, cardiopulmonary disease)
- Inadequate placental perfusion and/or gas exchange (eg, maternal hypertension or severe hypotension, placental insufficiency caused by vascular disease)
- Congenital infection or anomalies**(Graham et al., 2008)**

- **Intrapartum events:**

- Interruption of umbilical circulation (eg, true knot, cord prolapse, cord avulsion)
- Inadequate placental perfusion and/or gas exchange (eg, placental abruption, uterine rupture, severe maternal hypotension, abnormal uterine contractions)
- Traumatic delivery (eg, shoulder dystocia, difficult breech extraction)
- Abnormal maternal oxygenation (eg, pulmonary edema) **(Graham et al., 2008).**

- **Postnatal disorders:**

- Persistent pulmonary hypertension of the newborn .
- Severe circulatory insufficiency (eg, acute blood loss, septic shock)
- Congenital heart disease **(Graham et al., 2008).**

Infants at increased risk for perinatal asphyxia include those born to diabetic mothers or with severe intrauterine growth restriction (IUGR). In diabetic women, vascular disease, manifested by nephropathy, may contribute to the development of fetal hypoxia and subsequent perinatal asphyxia. Infants with severe IUGR who are deprived of oxygen and nutrients may have a difficult cardiopulmonary transition with perinatal asphyxia,meconium aspiration,and/or persistent pulmonary hypertension **(Graham et al., 2008).**

Physiological adjustment of the fetus to asphyxia:

In the case of life support for the newborn brain during the third stage of labour, an extremely complex switch occurs from placental life support to independent neonatal life support systems. The fetal/ neonatal life support switch involves radical anatomical and physiological changes, and to maintain neuron integrity during the switch (adequate brain perfusion with suitable blood), placental function is normally maintained until the newborn life support systems are functioning.The fetus and the newborn are much more resistant to hypoxia than adults because of the increased neonatal cardiac glycogen stores, the ability of the neonatal brain to utilize fatty acids as an energy sources and the vasodilator effect of carbon dioxide on the neonatal cerebral circulation **(Korthals and colon, 2005).**

Behavioral adjustment:

A reduction in fetal movements, whether body movements or breath movements, has been reported during asphyxia thus resulting in intrauterine growth retardation **(Mcintosh and stenson, 2004).**

Cardiovascular adjustment:

A-Acute hypoxemia (<30min.) in mature fetus causes:

- Immediate fall in fetal heart rate (bradycardia).
- Peripheral vasoconstriction and rise in arterial blood pressure.
- Increase in central venous pressure.
- Increase in myocardial contractility and slight increase in cardiac output **(Synder and Aurora, 2004).**

In response to hypoxic ischemic insults, Circulatory re-arrangement of cardiac output occurs, with shunting of blood flow away from liver, kidneys, gut, lung and skeletal muscles into the heart, brain and adrenal glands of infant. This shunting explains the coexistence of liver and kidney failure in cases of HIE **.** Although there is an increase of up to 100% in total cerebral blood flow (CBF) during episodes of fetal hypoxia, regional CBF also shows consistent adaptive changes. Blood flow to the brain is distributed towards more primitive regions, particularly the brain stem, at the expense of the cerebral cortices, thus protecting function in the most basic and vital centers **(Levene and De Vries, 2010).**

B- After 1-2 hours of hypoxemia:

The fetus compensate by increasing umbilical blood flow and increasing the proportion of oxygenated blood delivered by the umbilical vein and directed to the myocardium and brain during asphyxic episodes **(Rurak et al., 1990).**

C-Hypoxemia for 6-8 hours:

It causes progressive metabolic acidaemia, but both fetal oxygen consumption and cardiovascular performance are largely maintained until the PH falls below 6.9 **(synder and Aurora, 2004).**

D- In chronic hypoxemia:

Haemoglobin, blood volume, erythropoietin, cortisol, catecholamine and heart rate are all increased **(Gomella et al., 2004).**

3) Hormonal adjustment:

Catecholamines are secreted by the fetal adrenal glands in response to stress due to increased blood flow to adrenal. These substances may

mediate some of the vascular effects seen in the normal fetus during period of hypoxia. Both noradrenalin and adrenalin are released, stimulating receptors. Also during fetal stress high levels of fetal cortisol are produced **(McIntosh and Stenson, 2003).**

4) Autonomic adjustment:

The autonomic nervous system is closely involved with other fetal responses to stress as it shows differential maturation within the developing fetus. In the fetal lamb, parasympathetic activity shows a net cumulative over the sympathetic system, resulting in fetal bradycardia during episodes of hypoxic stress. In the newborn lamb, this has changed to give a net sympathetic response leading to tachycardia following hypoxic stress **(McIntosh and Stenson, 2003).**

Normally the fetal response to hypoxia is bradycardia. This is unlike the response in adults who respond by tachycardia. This fetal response is due to fact that the fetus in late pregnancy has well developed chemo receptors that can be immediately stimulated by hypoxia & lead to bradycardia via vagal nerve regulation i.e. Para-sympathetic predominance. Also the initial peripheral vasoconstriction increases the blood pressure and stimulates arterial baroreceptors that maintain bradycardia **(Kliegman et al., 2011).**

5) Metabolic adjustment:

Glucose and oxygen are the metabolic fuels of the developing brain. Metabolism can switch to anaerobic during periods of hypoxia using glucose and glycogen which becomes the vital source of additional energy when the oxygen reserve is insufficient to maintain aerobic metabolism. It soon leads to accumulation of lactic acid in tissues and

blood giving rise to an increasing acidemia. The mobilization of liver glycogen stores to increase blood glucose levels during hypoxia is important for the maintenance of brain and myocardial functions **(Volpe, 2001).**

pathophysiology

The majority of the underlying pathologic events of HIE are a result of impaired cerebral blood flow and oxygen delivery to the brain **(Shalak and Perlman, 2004).** However, the pathophysiologic effects of the hypoxic-ischemic insult are complex and evolve over time. The unfolding of signs and symptoms makes it difficult for health care providers to determine timely appropriate treatment options. The pathologic events of HIE occur in two phases: primary energy failure and secondary energy failure **(Cotten and Shankaran, 2010)** .

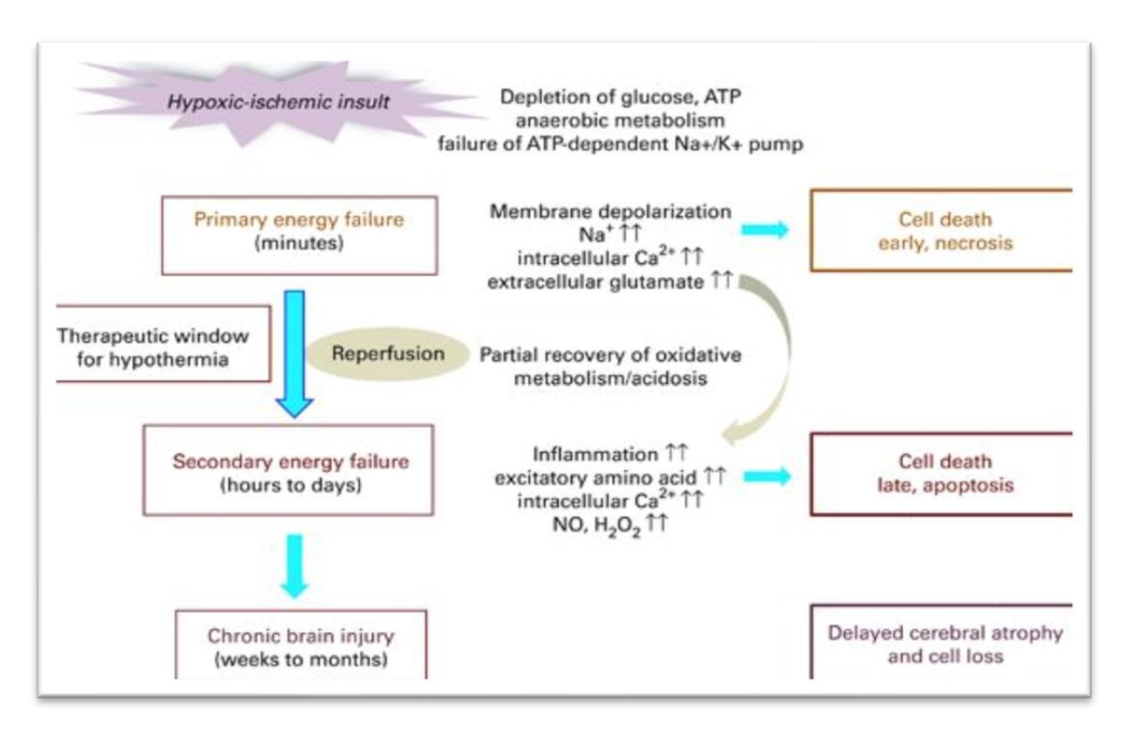


Figure 1. Algorithm demonstrates Mechanism of HIE (Johnston et al., 2011)

Primary Energy Failure:

Primary energy failure occurs as a result of the initial reduction of cerebral blood flow. The impairment of cerebral blood flow leads to decreases in oxygen and glucose, which leads to significantly less energy (adenosine triphosphate (ATP)) and increased lactate production **(Hanrahan et al., 1996)**. The low ATP levels cause failure of many of the mechanisms that maintain cell integrity, particularly the sodium/potassium (Na/K) pumps and mechanisms to maintain low intracellular calcium **(Volpe, 2008)** . When the Na/K pumps fail, an excessive influx of the positively charged sodium ions precipitate massive depolarization of neurons. This leads to the release of glutamate, a prominent excitatory neurotransmitter. The glutamate binds to glutamate receptors allowing additional influx of intracellular calcium and sodium **(Johnston et al., 2009) .**

Increased intracellular calcium has significant detrimental effects leading to cerebral edema, ischemia, microvascular damage with resultant necrosis and/or apoptosis. These two types of cell deaths occur in both primary and secondary energy failure. Most of the effects of the primary energy failure lead to cellular necrosis through impaired cellular integrity, disruption of the cytoskeleton and cell membrane **(Cotton and Shankaran, 2010).**

Necrosis occurs in conditions of very severe hypoxia and ischemia. This causes cells to swell and rupture leading to cellular death. Upon rupture, cellular contents are released with resulting in additional inflammation. When inflammation occurs there is an influx of microglia to the area, which release inflammatory mediators. The inflammatory mediators can damage white matter and lead to formation of scar tissue. If

the insult is less severe, the cells may recover or progress to apoptosis, programmed cell death **(Alvarez et al., 2007)** .

Apoptosis causes cell shrinkage and general preservation of the cellular membranes with no associated inflammation. The apoptosis can occur days following the initial injury. Both necrosis and apoptosis can lead to decreased brain function **(Fatemi et al., 2009)** .

The extent of primary energy failure contributes to further injury in the secondary energy failure phase. If the hypoxic ischemic insult is severe, neuronal cell death can occur through necrosis. Once blood flow is restored, there is a brief period of recovery **(Sahni., 2008)** . This brief recovery, the latent period, is characterized by normal cerebral metabolism.

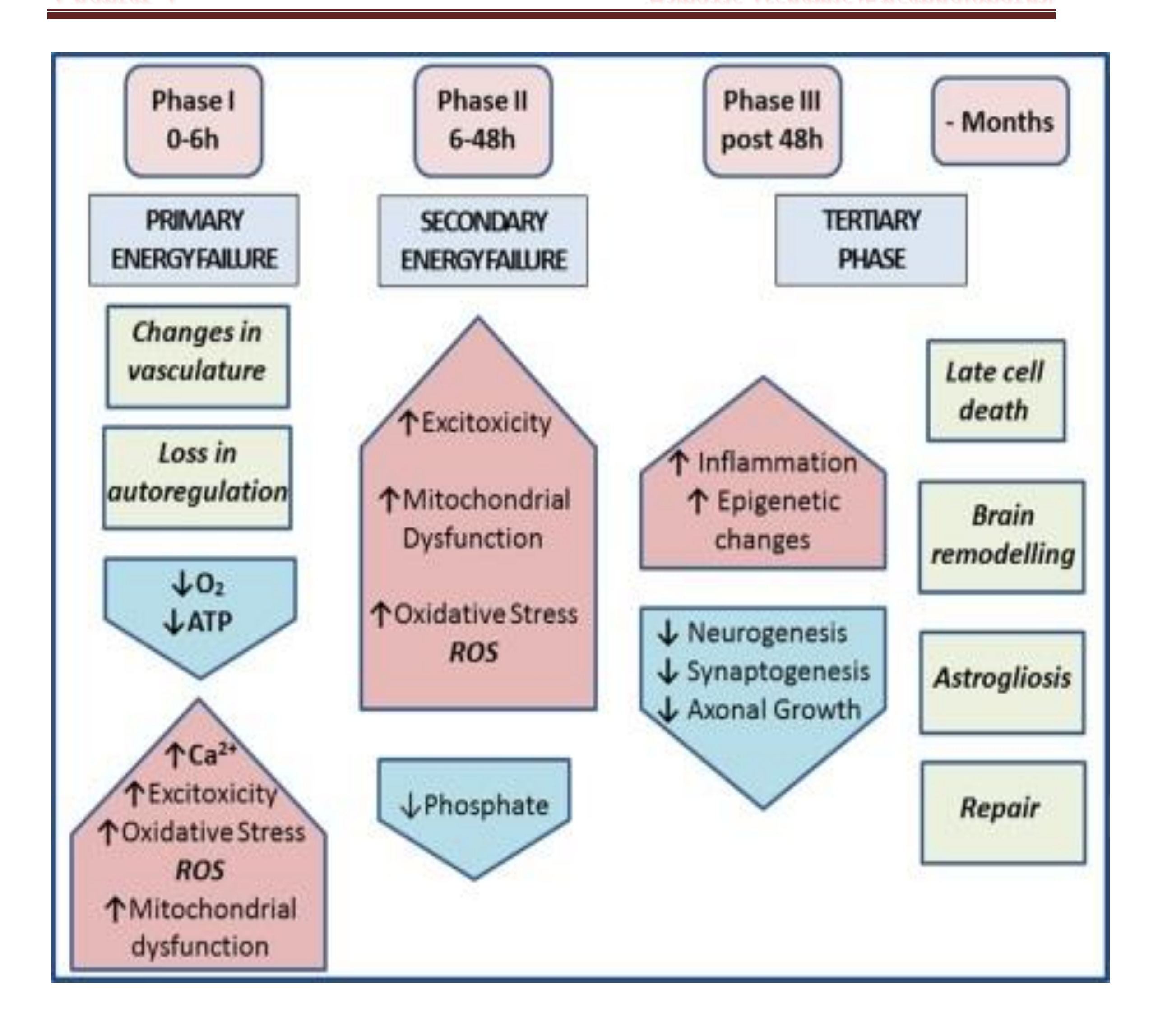


Figure 2. Algorithm shows phases of injury post HIE (Douglas, 2015)

The latent period is thought to vary depending on the extent of the severity of the hypoxic-ischemic insult. The more severe the insult, the shorter the latent period is **(Iwata et al., 2007)** . At this point, the exact timing of when the primary energy failure phase, the latent period, and the secondary energy failure phase begin and end remains unknown. The latent period is considered the optimal timing for therapeutic interventions **(Laptook, 2009)** .

Secondary Energy Failure:

The secondary energy failure phase occurs 6 to 48 hours after the initial injury. The exact mechanisms of secondary energy failure remain unclear but appear to be related to oxidative stress, excitotoxicity, and inflammation. The overproduction of free radicals, which cause damage to neuronal cell membranes and lead to necrosis or apoptosis cause oxidative stress. Oxidative stress is particularly harmful to the neonatal brain due to low concentrations of antioxidants and a high consumption of oxygen when transitioning from fetal to neonatal life **(Ferriero, 2004)**

Neonates also have high concentrations of unsaturated fatty acids that break down to form more oxygen free radicals. During a hypoxic-ischemic state, the iron that was bound to proteins is released, which makes the free iron (Fe^{2+}) available to react with peroxides and form free radicals. The decreased ability of the neonatal brain to eliminate free radicals and the increased susceptibility to the free radials leads to damage of neuronal tissue **(Buonocore, 2007)** .

Excitotoxicity occurs when excessive levels of extracellular neurotransmitters, especially glutamate, over stimulate excitatory receptors. The overstimulation allows additional influx of sodium and calcium into the neural cells. Glutamate is used by a variety of neuronal pathways including hearing, vision, somatosensory function, learning and memory, which can account for the disruptive effect of HIE on subsequent development. Inflammation is also thought to be important in the development of the HIE-related brain injury, but the exact mechanism remains unknown. Animal models suggest that infiltration of neutrophils into the cerebral tissue in the early stage of the injury (4–8 hours) lead to cerebral edema **(Palmer and Roberts, 2004)** .

TIMING OF INJURY

Asphyxia can occur before, during, or after birth. Based on a review of multiple studies that have examined the temporal relationship of obstetric events and neonatal outcomes, predominantly HIE in term infants, the proportion of conditions that occurs in each time period can be estimated. Antepartum events, such as maternal hypotension or trauma, account for 4 to 20 percent of cases. Intrapartum events, such as placental abruption or umbilical cord prolapse, are seen in 56 to 80 percent. Evidence of intrapartum disturbance (eg, meconium-stained amniotic fluid or severe fetal heart rate abnormalities) occurs in 10 to 35 percent, usually in association with an antenatal risk factor, such as diabetes mellitus, preeclampsia, or intrauterine growth restriction. In approximately 10 percent of cases, a postnatal insult occurs, usually caused by severe cardiopulmonary abnormalities or associated with prematurity. However, the timing of injury often is difficult to establish for an individual infant, in part because antepartum and intrapartum events may not lead to signs that are detectable in the fetus. In addition, a fetus who has suffered an antepartum insult may be at increased risk of incurring further intrapartum injury **(Volpe, 2008).**

Timing and Type of Brain Injury Patterns Based on Imaging Studies Consistent With an Etiology of an Acute Peripartum or Intrapartum Event:

1. Cranial ultrasonography lacks sensitivity for the common forms of brain injury in the encephalopathic newborn. However, if echodensity or echogenicity is detected on cranial ultrasonography, as it may be the only neuroimaging modality able to be obtained in a very unstable infant, it is observable 48 hours or longer after an ischemic cerebral

injury. Computed tomography lacks sensitivity for brain injury in the newborn and will often not reveal abnormalities in the first 24–48 hours after an injury.

2. MRI and magnetic resonance spectroscopy are the most sensitive neuroimaging modalities to assist with the timing of cerebral injury. MRI—combining conventional, diffusion, and spectroscopy—between 24 hours and 96 hours of life provides the most useful guide on the potential timing of a cerebral insult.

3. Diffusion abnormalities are most prominent between 24 hours and 96 hours of life. With conventional qualitative MRI, cerebral abnormalities will become most evident after 7 days from a cerebral injury. Two MRI or magnetic resonance spectroscopy scans—the first between 24 hours and 96 hours of life with emphasis on the evaluation of diffusion and spectroscopic abnormalities to assist in clinical management and evaluation of the timing of cerebral injury, and a second at day 10 of life or later—will assist with full delineation of the nature and extent of cerebral injury.

4. There are several well-defined patterns of brain injury and their evolution on MRI that are typical of hypoxic–ischemic cerebral injury in the newborn, including deep nuclear gray matter or watershed cortical injury. If a different pattern of brain injury or evolution of injury exists on MRI, then alternative diagnoses should be actively pursued (eg, metabolic and genetic investigations).

5. Certain patterns of brain injury seen on MRI—such as focal arterial infarction, venous infarction, isolated intraparenchymal or intraventricular hemorrhage, porencephaly, or atypical patterns of

metabolic encephalopathies suggest that peripartum hypoxia–ischemia did not play a role in causing neonatal encephalopathy.

6. Accurate interpretation of neuroimaging is important, and ongoing education in the interpretation and reporting of neonatal neuroimaging is encouraged. If there is limited expertise in neonatal neuroradiology and inconsistencies in the clinical profile of the infant, an expert opinion should be sought for the interpretation of the neuroimaging.

7. In the presence of cerebral injury that is diagnostically consistent with a hypoxic–ischemic pattern of injury, neuroimaging cannot determine the etiology of the hypoxia-ischemia, such as placental insufficiency or interruption of umbilical cord blood flow.

(American College of Obstetricians and Gynecologists, 2014)

Clinical manifestations :

Clinical signs and symptoms of neonatal HIE can be non-specific at birth and usually evolve over a period of days, but data suggest that infants at the highest risk for having suffered severe HIE can be identified with the reasonable reliability based on clinical findings. These findings include the evidence of intrapartum distress (foetal heart rate abnormality), severe foetal acidemia, severe functional depression (indicated by a low 5-minute Apgar score), the need for resuscitation in the delivery room, an abnormal early neurologic examination, and an abnormal electroencephalogram **(Ilves, 2012).**

1- CNS effects

Hypoxic ischemic encephalopathy (HIE) refers to the CNS dysfunction associated with perinatal sphyxia. HIE is of foremost concern

in an asphyxiated neonate because of its potential to cause serious long-term neuromotor sequelae among survivors. Common symptoms of HIE are hypotonia, poor feeding, seizures and a reduced level of consciousness **(Agarwal et al., 2008).**

Grades of HIE are:

- **Mild hypoxic-ischemic encephalopathy:**

The infant seems hyperalert, muscle tone may be slightly decreased initially, and deep tendon reflexes may be brisk during the first few days.Transient behavioral abnormalities, such as poor feeding, irritability, or excessive crying or sleepiness (typically in an alternating pattern), may be observed.Typically resolves in less than 24 hours without any consequences **(Ambalavanan et al., 2006)**.

- **Moderately hypoxic-ischemic encephalopathy:**

The infant is lethargic, with significant hypotonia and diminished deep tendon reflexes.The grasping, Moro, and sucking reflexes may be sluggish or absent.The infant may experience occasional periods of apnea.Seizures typically occur early within the first 24 hours after birth.Full recovery within 1-2 weeks is possible and is associated with a better long-term outcome.An initial period of well-being or mild hypoxic-ischemic encephalopathy may be followed by sudden deterioration, suggesting ongoing brain cell dysfunction, injury, and death, during this period, seizure intensity might increase **(Majeed et al., 2007).**

- **Severe hypoxic-ischemic encephlopathy:**

Stupor or coma is typical. The infant may not respond to any physical stimulus. Breathing may be irregular, and the infant often

requires ventilatory support.Generalized hypotonia and depressed deep tendon reflexes are common.Neonatal reflexes (eg, sucking, swallowing, grasping, Moro) are absent. Disturbances of ocular motion, such as deviation of the eyes, nystagmus, bobbing, and loss of "doll's eye" (ie, conjugate) movements may be revealed by cranial nerve examination. Pupils may be dilated, fixed, or poorly reactive to light. Seizures are delayed, can be severe and may be initially resistant to conventional treatments. The seizures are usually generalized, and their frequency may increase during the 24-48 hours after onset, correlating with the phase of reperfusion injury. As the injury progresses, seizures subside and the EEG becomes isoelectric or shows a burst suppression pattern. At that time, wakefulness may deteriorate further, and the fontanelle may bulge, suggesting increasing cerebral edema. Irregularities of heart rate and blood pressure (BP) are common during the period of reperfusion injury, as is death from cardiorespiratory failure. Infants who survive severe hypoxic-ischemic encephalopathy The level of alertness improves by days 4-5 of life. Hypotonia and feeding difficulties persist, requiring tube feeding for weeks to months **(Leuthner and Das, 2004).**

Multi organ dysfunction:

Asphyxia can lead to multiorgan dysfunction and a redistribution of cardiac output to maintain cerebral, cardiac, and adrenal perfusion while potentially compromising renal, gastrointestinal, and skin perfusion **(Durkan and Alexander, 2011).**

Myocardial dysfunction

Asphyxia may cause myocardial ischemia, which usually is transient, but result in cardiogenic shock and death. This condition typically presents as impaired contractility, decreased cardiac output and

tricuspid insufficiency, although some infants have signs of respiratory distress, heart failure, or shock **(Levene and De Vries, 2010).**

- **Clinical features :**

Physical examination in affected patients shows tachypnea, tachycardia, and hepatomegaly consistent with heart failure. Systemic blood pressure may be low and capillary refill delayed, reflecting reduced peripheral perfusion. However, normal blood pressure can be present in infants with poor cardiac output, a phenomenon related to elevated peripheral vascular resistance. Many infants have a systolic murmur that is loudest at the lower left sternal border, typical of tricuspid insufficiency **(Kluckow, 2011).**

- **Diagnosis :**

The chest radiograph typically shows cardiomegaly. The appearance of pulmonary blood flow depends upon whether the left or right ventricle is predominantly affected. If left heart failure predominates, the lung fields are usually diffusely hazy, with pulmonary venous congestion. If the right side is more affected, pulmonary blood flow may be reduced by right-to-left atrial shunting and pulmonary congestion may be absent. The ECG may show signs of ischemia, with diffuse ST-T wave changes. The most common finding is ST depression in the mid precordium, with persistently inverted T-waves over the left precordium. The diagnosis of myocardial dysfunction may be confirmed by echocardiographic findings of decreased left ventricular ejection fraction and decreased shortening fraction. It also distinguishes right-to-left atrial shunting caused by myocardial dysfunction due to persistent pulmonary hypertension of the newborn from asphyxia. No laboratory test reliably detects cardiac

damage in perinatal asphyxia. Cord blood levels of creatinine kinase and its MB fraction do not distinguish infants with and without asphyxia, are not specific for cardiac damage, and neonatal levels may be elevated in the first day of life due to gestation, weight, and type of delivery. However, elevation of cardiac troponin T levels is specific for cardiac damage, occurs early following asphyxia, and appears to correlate with the severity of asphyxia and neonatal outcome **(Matter et al., 2010).**

Renal dysfunction

Renal dysfunction often accompanies perinatal asphyxia. The presentation and course depend upon the severity and duration of the hypoxic-ischemic event. Severe asphyxia results in diffuse tubular dysfunction with impaired reabsorption of sodium and water and decreased glomerular filtration rate. A milder insult may cause a transient loss of renal concentrating ability **(Seri et al., 1998).**

- **Diagnosis :**

Acute renal failure, or acute kidney injury (AKI), can be difficult to diagnose following asphyxia for a variety of reasons, including the lack of a consensus definition. AKI should be suspected if the serum creatinine concentration is increased (>1.0 to 1.5 mg/dL, 88 to 133micromol/L) and/or the urine output is reduced (<0.5 mL/kg per hour). However, renal failure after perinatal asphyxia may be non-oliguric in up to 50 % of neonates, and serum creatinine level can be highly variable in the first days of life **(Durkan and Alexander, 2011).**

- **Pulmonary disorders**

Several pulmonary disorders are associated with perinatal asphyxia.They include pulmonary edema, acute respiratory distress syndrome, meconium aspiration syndrome and persistent pulmonary hypertension of the newborn **(Matter et al., 2010).**

- **Pulmonary edema:**

Pulmonary edema may occur due to myocardial dysfunction. Infants have signs of respiratory distress, including cyanosis, tachypnea, nasal flaring, and grunting. Signs of cardiac dysfunction typically are present. The chest radiograph shows an enlarged heart, normal to increased lung volume, and prominent hilar vascular markings. Infants with respiratory failure may require oxygen supplementation and/or mechanical ventilation, and treatment of the underlying myocardial dysfunction. The disorder resolves in a few days in most cases **(Bhatti and Kumar, 2014).**

Gastrointestinal dysfunction

Gastrointestinal complications after perinatal asphyxia include feeding intolerance, necrotizing enterocolitis, and hepatic dysfunction.

- **Feeding intolerance :**

Feeding intolerance may present as abdominal distension, delayed gastric emptying, and gagging. These abnormalities appear to be caused by transient disturbances in intestinal motor activity patterns, which may result from loss of neural regulation and/or inhibition of motor control **(Berseth and McCoy, 1992).**

- **Necrotizing enterocolitis :**

Alterations in intestinal blood flow can follow perinatal asphyxia and persist for up to three days. These changes may lead to ischemia and subsequent development of necrotizing enterocolitis (NEC). The incidence of NEC increases with decreasing gestational age. NEC typically presents after one week of age in premature infants, and in the first few days after birth in term infants. Signs include bloody stools, often with mucus **(Andrews et al., 1990).**

Hepatic dysfunction

Ischemia can interfere with synthetic, excretory, and detoxifying functions of the liver. These functions should be assessed. Transaminases frequently are elevated for several days after birth and reduced synthesis of clotting factors may result in prolongation of prothrombin and activated partial thromboplastin times, sometimes associated with clinical bleeding. Severely affected infants may develop hypoglycemia and serum glucose values should be monitored. Cholestatic jaundice or hyperammonemia may occur **(Karlsson et al., 2006).**

Hematologic disorders

Infants with perinatal asphyxia may have bleeding disorders. Causes include disseminated intravascular coagulation (DIC), impaired synthesis of clotting factors, and thrombocytopenia In particular, perinatal asphyxia is an associated risk factor for thrombocytopenia. The most important mechanism of thrombocytopenia probably is related to increased platelet destruction caused by DIC, although decreased production may contribute, The platelet count should be monitored and patients with thrombocytopenia or clinical bleeding should be evaluated

for DIC. Platelets and fresh frozen plasma can be provided as needed **(Bauman et al., 2011).**

Diagnostic Criteria

The 2003 guidelines from the American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) for hypoxic-ischemic encephalopathy (HIE) indicate that all of the following must be present for the designation of perinatal asphyxia severe enough to result in acute neurologic injury:

- Profound metabolic or mixed acidemia (pH < 7 or base deficit > 12 mmol/L) in an umbilical artery blood sample, if obtained.
- Persistence of an Apgar score of 0-3 for longer than 5 minutes.
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia).
- Multiple organ involvements (eg, kidney, lungs, liver, heart, intestines).

In rare instances, some babies will not fit the aforementioned criteria and the timing of the insult cannot be precisely known; however early magnetic resonance imaging of the brain can sometimes provide some insights **(AAP, 2003).**

Laboratory Studies

The diagnosis of hypoxic-ischemic encephalopathy (HIE) is made based on the history, physical and neurological examinations, and laboratory evidence. There are no specific tests to confirm or exclude a diagnosis. However, tests are performed to assess the severity of brain injury and to monitor the functional status of systemic organs**(Mir, 2014).**

➢ **Serum electrolyte levels**

In severe cases, daily assessment of serum electrolytes are valuable until the infant's status improves. Markedly low serum sodium, potassium, and chloride levels in the presence of reduced urine flow and excessive weight gain may indicate acute tubular damage or syndrome of inappropriate antidiuretic hormone (SIADH) secretion, particularly during the initial 2-3 days of life. Similar changes may be seen during recovery; increased urine flow may indicate ongoing tubular damage and excessive sodium loss relative to water loss **(Seri et al., 1998).**

➢ **Cardiac function studies**

A cardiac enzymatic study gives an estimation of the extent of cardiac injury from asphyxia **(Matter et al., 2010).**

➢ **Renal function studies**

Serum creatinine levels, creatinine clearance, and blood urea nitrogen (BUN) levels is affected in most cases. Evaluations of blood urea and serum creatinine levels are the tests most frequently used to assess renal injury caused by perinatal asphyxia. Currently, these indicators are not considered helpful to the early identification of renal damage. In fact, they reflect the glomerular damage, and the consequent reduction of glomerular filtration rate (GFR), that occurs at least 24 hours after the hypoxic insult and when about 50% of nephrons are compromised. Furthermore, serum creatinine level at birth reflects the maternal level. At present, more useful markers of kidney injury are available. Asphyxial insult causes an earlier and subtler damage of tubular cells, determining their necrosis. Accordingly, markers of tubular

dysfunction such as urinary β2 microglobulin have been found to be better indicators of early renal injury **(Banerjee, 2013).**

- **Liver enzymes**

These values are an adjuvant to assess the degree of hypoxic-ischemic injury to these other organs. These findings may also provide some insight into injuries to other organs, such as the liver **(Karlsson et al., 2006).**

- **Coagulation system evaluation**

This includes prothrombin time, partial thromboplastin time, fibrinogen levels, and serial platelet counts to assess the synthetic functions of the liver as well as assess for consumptive coagulopathy or bone marrow suppression **(Shastri et al., 2012).**

- **Blood Gases**

The clinical value of cord blood gas analysis lies in its ability to provide objective evidence of asphyxia at the moment of birth. It has been shown to be more reliable than routine clinical assessment at birth using the Apgar scoring system . Asphyxia is reduced tissue oxygen (hypoxia) of sufficient severity and duration to cause metabolic acidosis **(Low, 1997).**

Metabolic acidosis develops because when tissue cells are severely depleted of oxygen, aerobic metabolism of glucose is compromised, and cells must depend for their function and survival on less effective anaerobic pathways that result in reduced ATP (energy) production and, importantly for this discussion, accumulation of metabolic acids (principally lactic acid) **(Omo-Aghoja, 2014).**

Normal buffering mechanisms are overwhelmed by this acid influx, and pH falls below normal limits. Cord-blood metabolic acidosis – which is characterized by reduced blood pH and decreased base excess (i.e. increased base deficit) – thus implies that sometime during labor, oxygenation of fetal tissues was severely compromised. Umbilical cord blood gas analysis is now recommended in all high-risk deliveries by both the British and American Colleges of Obstetrics and Gynaecology and in some centres it is practised routinely following all deliveries **(American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2006).**

Since the incidence of HIE is much lower (around 1.5/1000 live births) than that of significant metabolic acidosis (0.5-1 % live births) **(Kurinczuk et al., 2010).** it is clear that HIE is not an inevitable consequence of significant metabolic acidosis. Indeed, most (around 75 %) babies with significant metabolic acidosis (pH <7.0, base excess <–12.0 mmol/L) do not suffer any signs of neurological illness or other adverse effects. In short, significant cord metabolic acidosis (pH <7.0 and base excess <–12 mmol/L) is necessary, but not sufficient to confirm that an acute intrapartum hypoxic event was the cause of encephalophy/cerebral palsy **(Liston, 2007).**

Immediately after birth, ideally before the baby's first breath, an approximate 20-cm segment of cord must be isolated between two sets of two clamps. Delay in clamping by as little as 45 seconds after birth results in significant change in acid-base parameters **(Mokorami et al., 2013)**. the longer the delay, the greater is the change **(Armstrong, 2006).** The change is a progressive decrease in pH and base excess and increase in pCO_2 and lactate.

This so-called “hidden acidosis” phenomenon is thought to be a transient physiological effect of initiation of neonatal breathing and can give a false impression of significant acidosis at birth **(Mokorami et al., 2013)**.

The close juxtaposition of arteries and vein in the umbilical cord makes it quite possible to sample venous blood in the mistaken belief that it is arterial blood **(Thorp et al., 1996).** Given these difficulties, it is widely recommended that blood from both artery and vein are sampled and analyzed **(American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2006).**

- **Markers of central nervous system damage**

The availability of markers of neurological damage may be very important to target therapy, evaluate response to treatment and predict neurodevelopmental outcomes. Therefore, many biomarkers of brain injury have been investigated in the past years. Hypoxia, both acute and chronic, is a well-known cause of an increased count of NRBC. Both NRBC count and NRBC count per 100 white blood cells (NRBC/100WBCs) have been found to be higher in those patients that exhibited a convulsion in the first 12 hours after birth and in those patients that subsequently developed HIE stage III. The newborns that died or those with sequelae had a significantly higher NRBC count **(Rai et al., 2014).**

In newborn term infants with intra-partum signs of foetal distress, the blood-plasma levels of lactate-dehydrogenase are considered as a good predictor of hypoxic-ischaemic encephalopathy during the first 12 h after birth. This result is of clinical interest offering a potential

inexpensive and safe prognostic marker in newborn infants with perinatal asphyxia **(Karlsson et al., 2010)**

Other markers seem to be related to neuronal damage associated with neonatal asphyxia. The neuron-specific enolase (NSE), normally produced by central and peripheral neurons, was found to be increased in serum immediately after birth in newborns with moderate or severe forms of HIE **(Celtik et al., 2004).**

At present, no specific and reliable markers of brain injury have been identified. Nevertheless, some biomarkers have shown to be involved in the hypoxic mechanism that leads to CNS damage. Glial fibrillary acid protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), normally expressed either in neurons and in astrocytes, are easily measurable markers of neuronal apoptosis **(Massaro et al., 2013).**

Several cytokines are released in acute HIE and their potential as early and accurate biomarkers is being extensively researched. Interleukin (IL)-6 and IL-16 in cord blood were found to be significantly associated with electrographic and clinical HIE severity in a study of full term infants **(Walsh et al., 2013).**

S100B is a calcium binding protein released by brain glial cells in response to injury. Elevated levels of S100B have been evaluated in cord blood **(Zaigham et al., 2017)** urine ,CSF, as well as amniotic fluid for newborns with HIE or encephalopathy. A recent clinical study elevated umbilical cord blood levels of this protein in neonates suffering from HIE stages II-III, suggesting that this biomarker may correlate with the severity of disease and the risk of adverse neurodevelopmental outcomes and/or death. Elevated S100B protein in plasma within 24 h after birth is

associated with increased brain injury as evaluated by MRI in a cohort of 50 newborns with HIE **(Massaro et al., 2018).**

- **To exclude other causes of neonatal encephalopathy consider:**

- Lumbar puncture .
- Blood for chromosome analysis, ammonia, amino acids .
- Urine for amino and organic acids, ketones, reducing substances .
- Early newborn screening test (NNST) if metabolic/genetic disorders suspected.
- Cranial ultrasound (CUS) **(Shah et al., 2004).**

- **Imaging in neonatal hypoxic–ischaemic brain injury:**

- **Cranial Ultrasonography**

MRI is predictive of long-term outcomes in patients with HIE in multiple studies. However, MRI is costly, lacks portability, is time consuming and consequently, is limited in its utility in nonacademic centers, in low-income countries and with critically ill patients who are too unstable to be moved. Brain US has emerged as a powerful, inexpensive adjunctive and alternative tool to MRI. US is widely available, can be performed bedside without sedation, can be repeated as often as necessary, has no side effects and when performed by an experienced sonographer using high-end equipment, provides a wealth of anatomical and functional information **(Martinez-Biarge et al., 2012).**

US has value as a screening tool in infants with HIE. However, it is not uncommon that significant abnormalities are not detected until 24–96

hr after birth **(Tann et al., 2016).** Thus HIE may not be immediately apparent and the predictive value of a normal head US in this early phase is low. If there is a significant abnormality already present at this stage (less than 24 h after birth), it is highly predictive of a poor outcome due to a particularly severe insult or because the injury occurred prior to the onset of labor **(Leijse, 2007).**

Rutherford et al. demonstrated that basal ganglia and thalamic changes are more likely to be visualized on MRI than US. Those infants who do have abnormalities on US develop significant motor deficits, particularly if abnormalities are also seen on MRI and lesions at the convexity of the brain require a linear high-resolution probe (14–16 MHz) for evaluation on US. Lesions in the cortex are much less likely to be seen on US compared to MRI **(Rutherford et al., 1994).** In comparison to autopsy findings, when US is performed less than 12 h before death, the sensitivity and specificity for thalamic lesions is 100 and 83%, respectively and for lesions in the cortex it is 76.9 and 100%, respectively **(Eken et al., 1994).**



Figure 3. Newborn with severe HIE (Guan, 2017).

Newborn with severe neonatal hypoxic-ischemic encephalopathy, Ultrasound examination shows hyperechoic and fuzzy brain parenchyma (arrows) in periventricular areas.

Sonography is sensitive for the detection of hemorrhage, periventricular leukomalacia (PVL), and hydrocephalus. Doppler interrogation and the assessment of resistive index (RI) provide additional information on cerebral perfusion. The RI is calculated from the peak systolic velocity and end diastolic velocity by the following formula: RI= (PSV-EDV)/PSV **(Fickenscher et al., 2012).** Normally, the RI decreases with increasing gestational age, and thus correlation with gestational age is necessary for accurate interpretation of RI results **(Kurmanavicius et al., 1997).**

Decreased RI is noted to be an abnormal finding and is postulated to be caused by impairment in cerebral autoregulation and subsequent decreased cerebrovascular resistence and increase in end-diastolic flow. However, sustained asphyxia with subsequent development of

intracranial hemorrhage or diffuse cerebral edema and loss of forward diastolic flow result in increased RI and is indicative of a poor outcome **(Benson et al., 2002).** Abnormalities in RI have been correlated with prognosis. An abnormal RI (equal to or less than 0.55), in the first 72 h after birth, has been found to be highly predictive of a poor prognosis with either death or severe disability **(Ilves et al., 2004).**

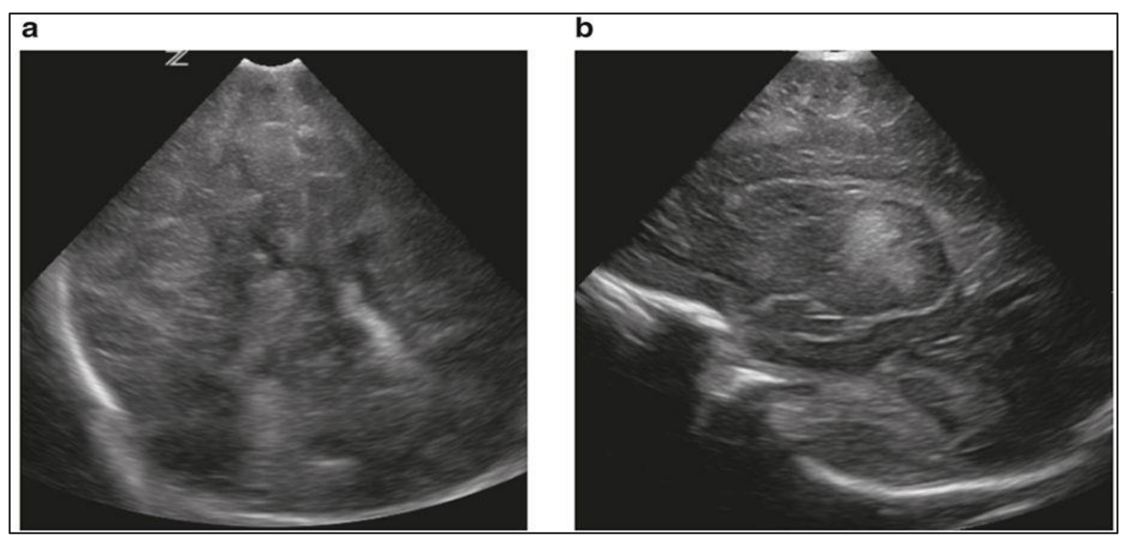


Figure 4. Cranial US in HIE (Cally Tann et al., 2016).

Severe dense echogenicity in the basal ganglia and thalami on parasagittal view (a) and global echogenicity and swelling in the white matter and cortex on coronal images (b) .

- **Brain magnetic resonance imaging (MRI)**

MRI is the imaging modality of choice for the diagnosis and follow-up of infants with moderate-to-severe hypoxic-ischemic encephalopathy **(Rutherford et al., 2010).** Conventional MRI sequences (T1w and T2w) provide information on the status of myelination and preexisting developmental defects of the brain. When performed after the first day (and particularly after day 4), conventional images may accurately demonstrate the injury pattern as area of hyperintensity. Conventional images are most helpful at age 7-10 days, when the diffusion-weighted

imaging (DWI) findings have pseudonormalized. Following a severe asphyxial event, a central pattern of injury is seen with injury to

(1) the deep gray matter (ie, putamina, ventrolateral thalamus, hippocampi, dorsal brainstem, or lateral geniculate nucleus)

(2) the perirolandic cortex. These areas contain the highest concentration of N-methyl-D-aspartate (NMDA) receptors and are actively myelinating **(Huang, 2008).**

Less severe or partial insult results in injury to the intervascular boundaries areas and is also called watershed injury. This type of lesions manifests in the infants as proximal extremity weakness or spasticity. Decreased signal in the posterior limb of the internal capsule (PLIC) on T1w images may be noted. The absence of normal signal (high intensity on T1w images) in the PLIC of infants older than 38 weeks' gestation is a strong predictor of abnormal motor outcomes in these infants **(Cowan and DeVries, 2005).**

DWI allows earlier identification of injury patterns in the first 24-48 hours. The MRI sequence identifies areas of edema and, hence, injured areas. DWI changes peak at 3-5 day and pseudonormalizes by the end of the first week. In neonates, DWI changes may underestimate the extent of injury, most likely because of the importance of apoptosis in the ultimate extent of neurologic injury **(Huang., 2008).**

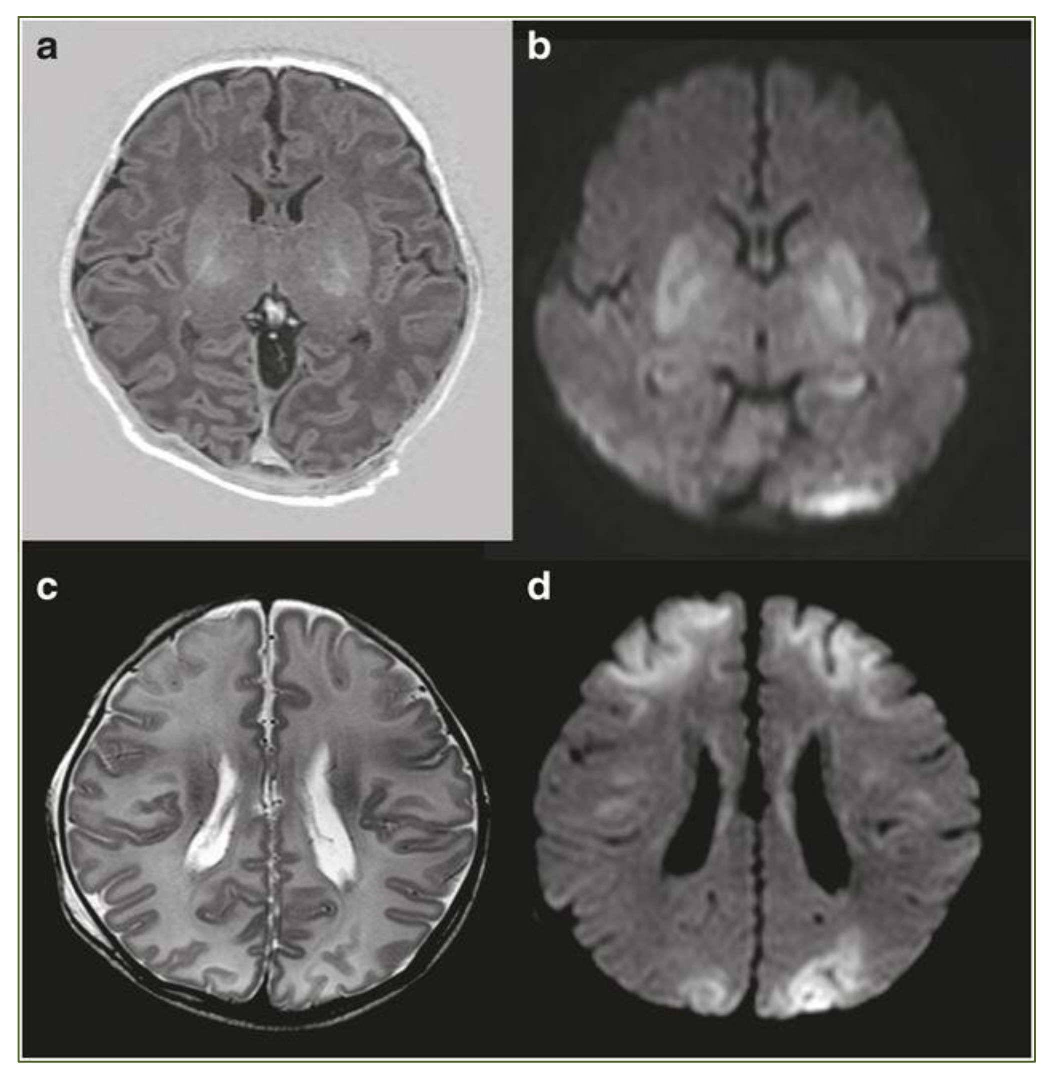


Figure 5. MRI finding in HIE (Robertson., 1990)

Different patterns of injury after perinatal asphyxia at term. Top row: axial T1-weighted magnetic resonance imaging (MRI) (**a**) and diffusion weighted imaging (DWI) (**b**) on day 4 in an infant with grade III encephalopathy. The T1-weighted MRI looks remarkably normal with some increased signal in the thalami, especially on the left. The signal in the posterior limb of the internal capsule appears to be present, especially on the right. This may be due to the fact that the MRI was performed early. Restricted diffusion is clearly seen on DWI in the basal ganglia bilaterally. Bottom row: axial T2-weighted MRI (**c**) and DWI (**d**) on day 5 of an infant with grade II encephalopathy. Signal changes can be seen in the watershed areas between anterior and middle, and also between the middle and posterior cerebral arteries. There is increased signal intensity and loss of the cortical ribbon on the T2-weighted MRI, especially in the right frontal lobe, but the abnormalities are easier to recognize with DWI.

MRI is also a useful tool in the determination of prognosis. Studies indicate that infants with predominant injuries to the basal ganglia or thalamus (BGT) have an unfavorable neurologic outcome when compared with infants with a white matter predominant pattern of injury. Abnormal signals in the PLIC have also been associated with poor neurologic outcome. Severe BGT lesions on early MRI (performed at a median of 10 d; range, 2-42 d) were strongly associated with motor impairment at 2 years. In addition, abnormal PLIC signal was also highly correlated with inability to walk independently at 2 years, with a sensitivity of 0.92 and a specificity of 0.77 **(Martinez et al., 2011).**

Both conventional images (T1- and T2-weighted) and diffusion techniques have a good specificity (>90%) and positive predictive value (>85%) in predicting death or major disability at age 2 years. However, sensitivity and negative predictive values are low **(Cheong et al., 2012).**

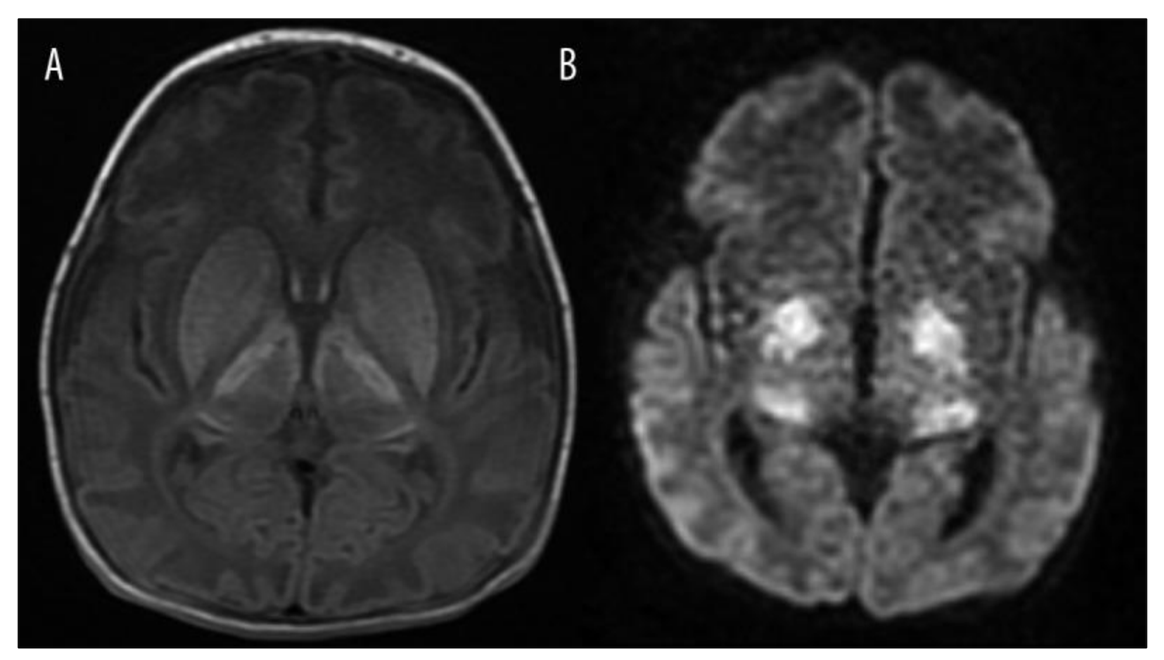


Figure 6. Acute asphyxia in MRI (Astra et al., 2012).

Injury of basal ganglia and thalamus in a term newborn – features of acute asphyxia. The lesions are hyperintense in all types of sequences (T1, T2, FLAIR) they show diffusion restriction. (A) SE/T1,ax; (B) DWI.

- **Near-infrared spectroscopy**

Near-infrared spectroscopy (NIRS) is a non-invasive tool for assessing cerebral hemodynamics and oxygenation. It has been documented that newborns with HIE may exhibit brain hyperperfusion early after birth, probably as a consequence of reperfusion injury . Therefore, the measurement of brain perfusion may be useful to assess and treat this category of newborns. MRI can offer this type of information but MRI scans are not easily obtained in critically-ill patients. NIRS represents a good alternative and complementary tool, since it permits cerebral hemodynamic monitoring at patient bedside, additionally, it is cheaper, can be easily used and is able to perform serial measurements of brain perfusion**(Wintermark, 2011).**

- **Head computed tomography (CT) scanning**

Head CT scanning is a rapid mode of screening and is very effective in detecting hemorrhage with the added advantage of limited sedation need. However, evidence suggests that even a single CT scan exposes children to potentially harmful radiation **(Pearce et al., 2012).** Additionally, CT scanning is not a sensitive modality for evaluation of HIE because of the high water content in the neonatal brain and the high protein content of the cerebrospinal fluid, which result in poor parenchymal contrast resolution. Because of these concerns and owing to the superiority of MRI in evaluating brain structures, head CT scanning is not recommended in the evaluation of neonates with HIE **(Barkovich, 1997).**

- **Echocardiography**

Obtain an echocardiogram to evaluate the cardiac contractility and ejection fraction. Note that neonates with HIE receiving therapeutic hypothermia may experience a reduction in cardiac output and descending aorta blood flow. Systemic organ perfusion and cerebral metabolism may be affected by preferential cerebral distribution of cardiac output in conjunction with an increase in systemic peripheral vascular resistance **(Yoon et al., 2018).**

- **Electroencephalography and cerebral function Monitoring**

Different tools are available to study electric function of the neonatal brain, in particular standard electroencephalography (EEG) and cerebral function monitoring (CFM). A recent study has evaluated the relation between EEG patterns and neurological outcomes in term newborns with HIE, showing that a normal EEG is correlated with a normal outcome, whereas the presence of "burst suppression" on EEG is predictive of death or pathological outcome **(Jose et al., 2013).**

Sequential EEG, in newborns with seizures, has been found to have more predictive value to estimate the neurological outcome and postnatal death, as compared to a single EEG recording **(Khan, 2008).**

The CFM is a real-time monitoring device that uses a method known as amplitude-integrated EEG (aEEG). This method consists of recording a single-channel EEG from biparietal or central electrodes. CFM is commonly used for bedside monitoring of background neurological activity in term and near-term infants with encephalopathy. CFM patterns are well correlated with those obtained with regular EEG, even though short or low amplitude seizures cannot be detected with CFM. Therefore,

CFM should never replace regular EEG and a standard EEG is always recommended in newborns with HIE. CFM has been shown to be useful to assess asphyxiated newborns in combination with neurologic examination and to select and manage those infants requiring particular treatments such as hypothermia. CFM can reveal different patterns: abnormal ones in the first 6 hours of life identify newborns with a worse outcome (death or disability); conversely, normal voltage patterns are associated with normal development **(Hellstrom, 2006).**

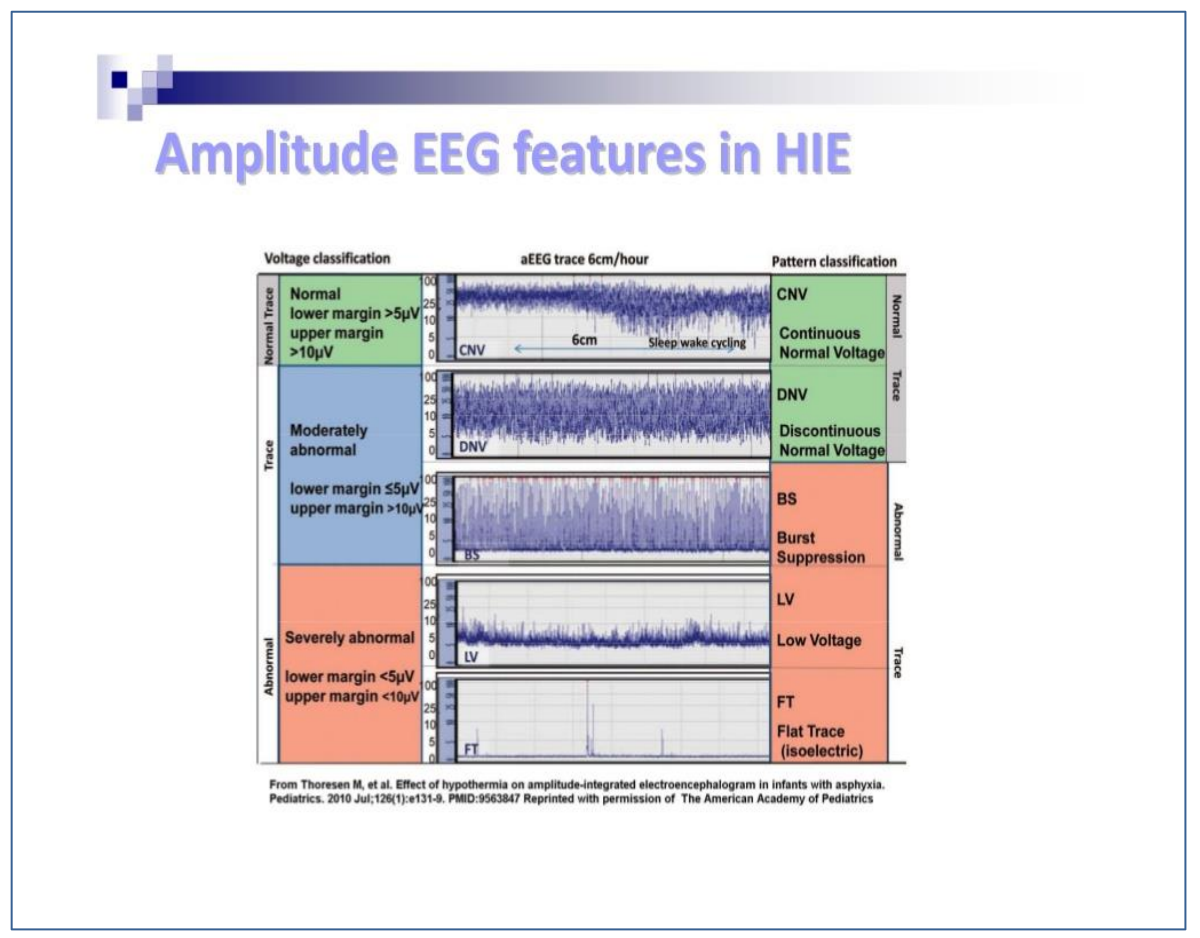


Figure 7. Different EEG pattern (Thoresan., 2010)

Management

The primary goal of medical care is Good prenatal care and management of medical condition e.g. maternal diabetes are the most important means of early reduction in the risk of HIE and preterm labor **(DeMenezes and Shaw, 2003).**

✓ Initial Resuscitation and Stabilization

Delivery room management follows standard Neonatal Resuscitation Program (NRP) guidelines. Close attention should be paid to appropriate oxygen delivery, perfusion status, avoidance of hypoglycemia and hyperglycemia, as well as avoidance of hyperthermia. A lot of attention has been focused on resuscitation with room air versus 100% oxygen in the delivery room. Several clinical trials indicate that room air resuscitation for infants with perinatal asphyxia is as effective as resuscitation with 100% oxygen. Based on this evidence, International Liaison Committee on Resuscitation (ILCOR) and NRP guidelines were updated and are now recommending the use of 21% oxygen for the initial resuscitation of term infants. If despite effective ventilation, the infant does not improve, higher concentrations of oxygen should be used and should be guided by the use of pulse oximetry **(Biban et al., 2011).**

✓ Supportive care

- Infants with HIE may have a degree of multiorgan dysfunction. The hypoxic fetus will initiate the diving reflex to preserve blood flow to vital organs, including brain, heart and adrenals, at the expense of flow to skin, splanchnic vessels, liver and kidneys **.** supportive care to the infant with HIE in the neonatal intensive care unit should reflect possible hypoxic damage to the organs and be individually tailored.

Acute tubular necrosis and syndrome of inappropriate antidiuretic hormone are common, Hence routinely monitor for electrolyte imbalance ,the urinary concentration together with daily fluid balance should be applied. Assessment of the state of hydration in severely oliguric patient may be facilitated by measuring the central venous pressure. Parenteral fluids should be restricted initially as infants will be oliguric; we would restrict fluids to 40 mL/kg/day typically until the urine output starts to increase. We administer parenteral nutrition through a central venous catheter **(Shah et al., 2004).**

- Trophic feeds may be started as colostrum becomes available; typically the feed volume does not increase above trophic feeds until after rewarming when the infant is less sedated. Medications requiring renal and hepatic metabolism, especially those with nephrotoxicity, should be used cautiously **(Basu, 2016)**.

- Hyperglycaemia and hypoglycaemia should be avoided, as both are associated with long-term disability at 18 months or death in infants with moderate to severe HIE **(Basu, 2016).** Some studies suggest the particular association of hypoglycaemia with adverse outcome and the operational threshold for taking steps to raise the blood glucose is higher in infants with HIE than healthy term infants (>2.5 mmol/L vs >2.0 mmol/L) **(Nadeem et al., 2011)**.

- Coagulopathy due to hypoxic-ischaemic injury to the liver and bone marrow may occur. Additionally hypothermia reduces platelet aggregation, reduces enzymatic function in the coagulation cascade and can trigger disseminated intravascular coagulation. Coagulation studies should be monitored daily during cooling as laboratory evidence of coagulopathy is universal in babies with HIE, undergoing

cooling. Transfusion strategies to maintain platelet counts >130×10^9/L, fibrinogen >1.5 g/L and INR <2 may prevent clinical bleeding **(Forman et al., 2014).**

- Hypotension is observed in up to 62% of infants with HIE, inotropic support for HIE has been recently reviewed **(Armstrong et al., 2012).** Studies indicate that a mean blood pressure (BP) above 35-40 mm Hg is necessary to avoid decreased cerebral perfusion. Dopamine or dobutamine can be used to achieve adequate cardiac output in these patients. If a cardiac injury is suspected, then administration of dobutamine or milrinone may be beneficial to support the injured heart. Cardiac troponins I and T are established markers of myocardial ischaemia and cardiac failure in adults, children and neonates. In HIE, troponin T levels have been shown to reach a peak on day 1, remain elevated for the first week and correlate with the severity of HIE **(Güneś et al., 2005).** Therapeutic hypothermia reduces cardiac output by 67% and an increase in support will usually be required doing the cooling period **(Armstrong, 2012).**

- Most infants with severe hypoxic-ischemic encephalopathy (HIE) need ventilatory support during the first few days after birth. Adequacy of ventilation should be closely monitored and PaO_2 and partial pressure of carbon dioxide kept within normal range. Evidence indicates that increased FiO2 in the first 6 hours of life is a significant risk factor for adverse outcomes in infants with hypoxic-ischemic encephalopathy treated with hypothermia therapy **(Sabir et al., 2012).** Acidosis and hypoxia should be corrected to avoid additional brain injury and PPHN, hyperoxia and hypocarbia should be avoided as they are detrimental to long-term outcome **(Pappas et al., 2011).**

Inhaled nitric oxide (iNO) may be used according to published guidelines if pulmonary hypertension is suspected **(AAP, 2000).**

✓ **Treatment of Seizures**

Hypoxic-ischemic encephalopathy (HIE) is the most common cause of seizures in the neonatal period. Even with therapeutic hypothermia for neuroprotection, about 50 percent of newborns with hypoxic ischemic encephalopathy have electrographic seizures **(Glass et al., 2014)** .

They usually occur 12-24 hours after birth and are difficult to control with anticonvulsants . Seizures are generally self-limited to the first days after birth but may significantly compromise other body functions, such as maintenance of ventilation, oxygenation, and blood pressure. Additionally, studies suggest that seizures, including asymptomatic electrographic seizures, may contribute to brain injury and increase the risk of subsequent epilepsy **(Holmes, 2005).**

Large, unilateral infarcts occur with neonatal seizures in as many as 80% of patients. Seizures are often partial (focal) and contralateral to the cortical lesion. About two thirds of newborns with cerebral venous infarcts have seizures. Those with multiple or diffuse lesions and cerebral venous infarcts often have multifocal or migratory seizures. Seizures are observed during physical examination and may confirm the diagnosis. Observation often reveals clonic rhythmic contractions. When holding the limb affected by clonic seizures, the examiner's hand shakes or feels limb movement. Generalized tonic posturing (eg, extension of the upper and lower extremities or extension of the legs and flexion of the arms) is related to an EEG seizure in 15% of affected neonates. Subtle seizures may be a part of the HIE picture. Subtle manifestations of neonatal seizures are confirmed on EEG and include apnea, tonic eye deviation,

sustained eye opening, slow, rhythmic, tongue thrusting, and boxing, bicycling, and swimming movements **(Hahn and Olson, 2004).**

Challenges in diagnosis are a major obstacle to treatment of neonatal seizures. Clinical diagnosis is not reliable because seizures in neonates are often subclinical (sometimes named silent, occult, or electrographic-only seizures) and because manifestations are often difficult to distinguish from other movements in babies **(Glass et al., 2016).** Furthermore, the phenomenon of electroclinical dissociation or uncoupling means that clinical seizure will become subclinical following drug administration **(Scher et al., 2003).** The gold standard for diagnosis is continuous electroencephalogram (cEEG) video monitoring **(Shellhaas et al., 2011).** In clinical settings where cEEG is not available, amplitude integrated EEG (aEEG) may be used.

Current therapies available to treat neonates with seizures have limited efficacy, and safety concerns remain specifically for infants undergoing therapeutic hypothermia . Antiseizure drugs used in this population include phenobarbital, levetiracetam, phenytoin, lidocaine, and benzodiazepines. However, phenobarbital has been shown to be effective in only 29-50% of cases **(Boylan et al., 2004)** and phenytoin only offers an additional 15% efficacy. Benzodiazepines, particularly lorazepam, may offer some additional efficacy. Newer antiseizure medications such as levetiracetam and topiramate are increasingly used in infants with HIE and seizures despite the lack of strong evidence regarding safety or efficacy in this population. Lidocaine may be effective in refractory neonatal seizures, but its use may be limited by potential cardiac toxicity **(Castro, 2005).**

1. Phenobarbital

The World Health Organization (WHO) guidelines recommended that phenobarbital should be used as the first-line agent for the treatment of neonatal seizures . Phenobarbital enhances gamma-aminobutyric acid A receptor ($GABA_A$) inhibitory activity, and may limit glutamate excitation . Phenobarbital is metabolized by the liver and excreted via the kidneys; therefore these processes may be impaired in neonates with hepatic or renal dysfunction after HIE. The usual loading dose of phenobarbital is 20 mg/kg given intravenously, and may be repeated if needed. The initial maintenance dose is 3–5 mg/kg/day, which can be given orally or intravenously **(Bialer, 2010).**

2. Phenytoin

Phenytoin is a sodium channel blocker Phenytoin acts by stabilizing sodium channels and reducing electrical conductance across the membrane.The usual loading dose of phenytoin 15–20 mg/kg given intravenously is recommended and Maintenance dosing is 4–8 mg/kg/day **(Bialer, 2010).**

3. Benzodiazepines

Benzodiazepines are GABA agonists at the $GABA_A$ receptors; this resuls in sedative-hypnotic, anxiolytic and muscle relaxant effects. Diazepam, lorazepam, clobazam, midazolam. Benzodiazepines have a rapid onset of action and a short duration of effect **(Mihi, 2011).**

4. Levetiracetam

Levetiracetam has efficacy as both monotherapy **(Stephen et al., 2011)** and adjunctive therapy for patients as young as 4 years of age

(Verrotti, 2010). Despite limited data on children less than 1 year of age, off-label use is employed. It may be administered as either a tablet or intravenous formulation**.** The data available are mostly from retrospective case studies and indicate levetiracetam has good efficacy as a second-line medication for seizures refractory to phenobarbital **(Abend et al., 2010).**

✓ **Hypothermia Therapy(Cooling)**

Extensive experimental data suggest that mild hypothermia (3-4°C below baseline temperature) applied within a few hours (no later than 6 h) of injury is neuroprotective. Therapeutic hypothermia when applied within 6 hours of birth and maintained for 72 hours is the only therapy currently available that improves the outcomes of infants with moderate-to-severe HIE**(Laptook, 2009).**The neuroprotective mechanisms are not completely understood. Possible mechanisms include:

(1) reduced metabolic rate and energy depletion.

(2) decreased excitatory transmitter release.

(3) reduced alterations in ion flux.

(4) reduced apoptosis due to hypoxic-ischemic encephalopathy.

(5) reduced vascular permeability, edema, and disruptions of blood-brain barrier functions **(Gunn, 2000).**

- **Inclusion criteria :**

➢ Near-term infants born at 36 weeks' gestation or more with birth weight of 1800-2000 g or more, younger than 6 hours at admission.

➢ Evidence of acute event around the time of birth Apgar score of 5 or less at 10 minutes after birth severe acidosis, defined as pH level of

less than 7 or base deficit of 16 mmol/L or less (cord blood or any blood gas obtained within 1 h of birth), continued need for assisted ventilation or ongoing resuscitation at 10 minutes after birth.

- Evidence of moderate to severe encephalopathy at birth – Clinically determined at least 2 of the following: Lethargy, stupor, or coma.
- Abnormal tone or posture.
- Abnormal reflexes [suck, grasp, Moro, gag, stretch reflexes].
- Decreased or absent spontaneous activity.
- Autonomic dysfunction [including bradycardia, abnormal pupils, apneas] and clinical evidence of seizures.
- Moderately or severely abnormal amplitude-integrated electroencephalography (aEEG) background or seizures **(Shankaran et al., 2005).**

- **Exclusion Criteria:**

- Major congenital abnormalities identified
- Suspected neuromuscular disorders .
- Suspected chromosomal abnormalities .
- Life threatening abnormalities of the cardiovascular or respiratory systems.
- Uncontrolled pulmonary hypertension.
- Critical bleeding or coagulopathy **(Smit, 2015).**

Method of Cooling:

Two methods have been used in clinical trials: selective head cooling and whole body cooling.




figure 8. Total body cooling vs Head cooling (Robert, 2016)

- In selective head cooling, a cap (Cool Cap) with channels for circulating cold water is placed over the infant's head, and a pumping device facilitates continuous circulation of cold water. Nasopharyngeal or rectal temperature is then maintained at 34º-35°C for 72 hours.

- In whole body hypothermia, the infant is placed on a commercially available cooling blanket, through which circulating cold water flows, so that the desired level of hypothermia is reached quickly and maintained for 72 hours .However, whole body hypothermia is most widely used modality to provide therapeutic hypothermia**(Shankaran et al., 2014).**

Adverse effects:

Many theoretical concerns surround hypothermia and its side effects, which include coagulation defects, leukocyte malfunctions, pulmonary

hypertension, worsening of metabolic acidosis, and abnormalities of cardiac rhythm, especially during rewarming **(Shankaran et al., 2008).**

Rewarming

The speed of rewarming remains controversial. In randomized clinical trials, infants were rewarmed over 6 to 12 hours (0.5°C every 1 to 2 hours). Most centres rewarm infants by 0.5°C every 1 to 2 hours. Seizures and worsening of clinical encephalopathy upon rewarming have been reported. In such circumstances, experts suggest recooling for 24 hours and resuming rewarming **(Kendall et al., 2012).**

✓ Neuroprotective Strategies

Several groups are investigating other neuroprotective strategies whether alone or in combination with hypothermia therapy include the following:

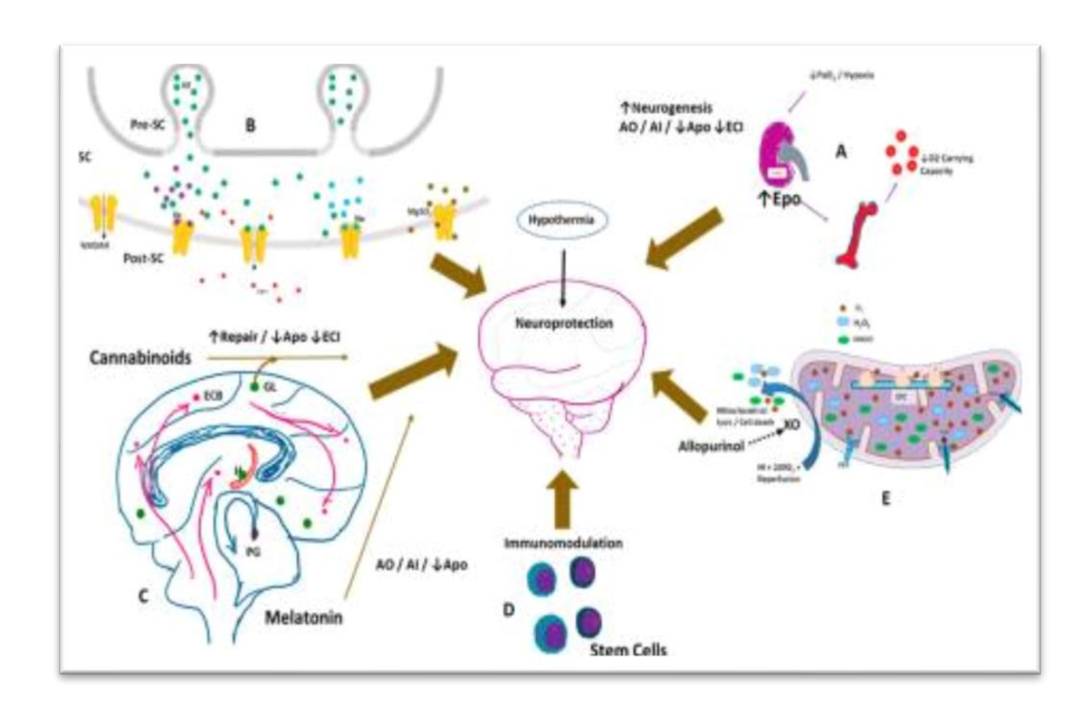


Figure 9. Neuroprotecctive strategies (Jayasree and Vasantha, 2018)

- Prophylactic barbiturates: In a small randomized trial, high-dose phenobarbital (40 mg/kg) was given over 1 hour to infants with severe hypoxic-ischemic encephalopathy. Treated infants had fewer seizures (9 of 15) than untreated control infants (14 of 16). Treated infants also had fewer neurologic deficits at age 3 years (4 of 15) than untreated infants (13 of 16) **(Hall et al., 1998).** In another small study, thiopental given within 2 hours and over 24 hours,did not result in improved rate of seizures or neurodevelopmental outcomes at 12 months. Hypotension was more common in infants who received thiopental. Thus, the role of prophylactic barbiturate remains unclear. Further studies are needed **(Evans et al., 2007).**

- Epo and EpoR are upregulated following hypoxic ischemic injury and Epo has an anti-oxidant as well as anti-inflammatory effect. It reduced apoptotic] and excitotoxic cell injury. A Phase I trial evaluating effective dose and safety demonstrated that a moderately high dose of 1000 U/kg achieved levels (based on animal studies) that would protective maximal neuroprotection and minimize risks of excessive Epo. In a Phase II double-blinded, placebo-controlled trial in infants undergoing TH for HIE, multiple doses of Epo (1000 U/kg) resulted in less MRI brain injury and potential for improved short-term motor outcomes **(Wu et al., 2016).** A Phase III trial evaluating the effect of Epo with TH on the combined outcome of death or neurodevelopmental disability is currently underway **(Juul et al., 2018).**

- Melatonin is an endogenous neuroendocrine moiety secreted by the pineal gland and well known for its role in modulating the circadian rhythm. Besides this, melatonin has several other mechanisms that suggest an important role in recovery and repair from brain injury.

Melatonin plays an important role in normal glial development and has anti-apoptotic , anti-inflammatory, and anti-oxidant effects. In a piglet model of neonatal HI injury, melatonin used along with hypothermia greatly decreased the HI-induced injury measured by magnetic resonance spectroscopy **(Robertson et al., 2013).**

- Allopurinol: Oxidant injury by free radicals and superoxides formed through activation of the xanthine oxidase pathway contribute to the damage caused by a hypoxic ischemic insult. Allopurinol is a xanthine oxidase inhibitor that is being investigated as a potential agent for use in treatment of HIE. Preclinical studies in various rodent and mammalian models of HIE have shown neuroprotective effects with use alone and recently, as a complement to TH **(Rodriguez et al., 2017).**

- Excitatory amino acid (EAA) antagonists: MK-801, an EAA antagonist, has shown promising results in experimental animals and in a limited number of adult trials. However, this drug has serious cardiovascular adverse effects **(Cotten et al., 2014).**

✓ **Other adjuvant therapies under investigation include**

- Xenon which is an anesthetic gas that crosses the blood brain barrier and is thought to act as an antagonist at glycine site of NMDA receptors and reduce neurotransmitter release **(Faulkner et al., 2011).**

- Argon: This is another significantly less expensive noble gas, that has demonstrated significant neuroprotection in animal models of HIE. They demonstrated reduced brain cell death, and aEEG improvements with combined argon hypothermia treatment **(Azzopardi et al., 2016).**

- Gangliosides are sphingolipids that serve an important function in maintaining cell membrane integrity. Monosialoganglioside therapy has been shown to protect against apoptotic injury and attenuate brain injury. This led to consideration of monosialogangliosides as an adjuvant therapy in HIE. In a meta-analysis of all published clinical studies, consisting of 787 neonates. They concluded that adjuvant treatment with monosialoganglioside potentially offers additional benefits in terms of improving short-term clinical effects and reducing long-term neurodevelopmental disabilities **(Sheng and Li, 2017).**

- A meta-analysis of five small randomized controlled trials evaluating $MgSO_4$ in HIE concluded that there was improvement in short-term outcomes without significant increase in side effects **(Tagin et al., 2013).**However, there is a need for large well designed studies to determine if there are long-term benefits of magnesium and to confirm its safety. Though generally considered a safe medication, there is some concern regarding risk of hypotension and bradycardia, especially with high doses of this medication which could limit its use **(Lingam and Robertson, 2018).**

- Topiramate blocks the voltage-dependent sodium and calcium channels and also inhibits the excitatory glutamate pathway while enhancing the inhibitory effects of gamma-aminobutyric acid (GABA)**.** Although administration of topiramate in newborns with HIE is safe, it did not reduce the combined frequency of mortality and severe neurological disability **(Filippi, 2018).**

- Preclinical studies in models of ischemic stroke have revealed that azithromycin has a neuroprotective effect . Recent abstracts have

investigated the possibility of using azithromycin in neonatal HIE alone and as an adjunct to hypothermia **(Barks et al., 2018**).

- Stem cell therapies appear to hold significant potential for newborns with NE based on animal data demonstrating neuroprotection from hypoxic ischemic brain injury. Umbilical cord blood (UCB) and tissue derived (Wharton jelly) cells, which contain endothelial progenitor cells, mesenchymal stem cells, and UCB-mononuclear cells, are an attractive therapy given their ease of acquisition from cord blood at birth. Neural stem-like cells have been derived from human UCBs, Cord blood stem cell therapy has could have protective effects mainly on inflammation, apoptosis, oxidative stress, and may enhance regeneration **(Nabetani et al., 2018).** However, whether these UCB-derived progenitors may be effectively differentiated into functional neuron-like cells in human newborns with brain injury remains unknown **(Van Pham, 2016).**

- The 5-day regimen of valproic acid administration resulted in some protective and therapeutic effects on the brain damage and neuronal apoptosis in both hemispheres in a dose-dependent manner. Administration of valproic acid also decreased the percentage of apoptotic neurons in the contralateral hemisphere These results suggest that valproic acid can have therapeutic and protective effects in hypoxic-ischemic brain injury **(Nimet et al., 2005).**

Long-Term Monitoring (Robertson, 2006)

- Growth parameters including head circumference should be closely monitored.
- Infants with moderate-to-severe HIE should be followed closely after neonatal intensive care unit (NICU) discharge by a developmental pediatrician and, in some cases,a pediatric neurologist. Early assessments (at 4–8 months) focus on head growth, general health and motor neurodevelopment. Assessments at 12–24 months focus on cognitive skills and language development. Preschool assessments are also strongly recommended to provide for the identification of children requiring early education programmes.
- Evaluation by a pediatric ophthalmologist is recommended during the first year of life.
- Standard hearing test screening should occur prior to NICU discharge.

Prognostic factors

The following criteria have been shown to be the most helpful in outlining likely outcomes**(Patel and Edwards, 1997):**

- Lack of spontaneous respiratory effort within 20-30 minutes of birth is almost always associated with death.
- The presence of seizures is an ominous sign.
- Abnormal clinical neurologic findings persisting beyond the first 7-10 days of life .
- EEG at about 7 days that reveals normal background activity is a good prognostic sign.
- Persistent feeding difficulties.
- Poor head growth during the postnatal period and the first year of life

Acute kidney injury is a common consequence of perinatal asphyxia, occurring in up to 56% of these infants. Therefore, the pathology specific biomarkers are of great clinical value being currently under extensive consideration by researchers**(Durkan, 2011).**

S100B is considered as one of the most potent blood-markers, significantly increased in blood serum 24 h after severe birth asphyxia insult in newborns**(Murabayashi et al., 2008).**

The use of therapeutic hypothermia changes the prognostic value of clinical evaluation in infants with HIE, and its impact on predicting outcomes is still under evaluation **(Gunn et al., 2008).**

Thompson score

Introduction

Currently, perinatal asphyxia associated with moderate or severe HIE, which is its main complication, affects between 1-2/1,000 live births in developed countries and is estimated at affecting between 10-20/1,000 live births in poor or developing countries, being responsible for 1/3 of neonatal mortality in these countries. However, we believe that the actual incidence of HIE in poor and/or developing countries is unknown. There are several factors making us unaware of our HIE rate.These include the difficulty presented by health teams to assess the newborns neurologically. A total lack of preparedness among health teams in relation to the use of neurological scores for the newborn or the total lack of their use at some centers is prevalent **(Lawn, 2005)** .

These are some of the factors leading us to believe that the actual incidence of HIE is higher than that already published. Having an easy-to-use clinical evaluation mechanism from the moment of birth would favor the obtainment of a more realistic notion of the importance of this pathology in all developing countries **(Perez, 2015).**

Several new technologies have become available to determine cerebral damage during perinatal period and predict long-term neurological outcome. These include computer (CT) scanning, magnetic resonance imaging (MRI), cerebral function monitoring, cranial ultrasound scanning and Doppler ultrasound of the middle cerebral artery **(Toh, 2000).**

These modalities are however not readily available in many neonatal units in developing countries. It requires additional training for medical and paramedical personnel and requires equipment. It is not ideal for implementation at any district or rural facility where special investigations and indeed specialist paediatricians are unavailable. The Hypoxic Ischemic Encephalopathy (HIE) score is a clinical tool comprising of a set of clinical signs associated with central nervous system (CNS) dysfunction. It is used to assess status of a child following birth asphyxia. There are various HIE scoring systems **(Sarnat, 1976).**

HIE scoring systems was originally described by Amiel-tison **(Amiel, 1969)** followed by numerous other grading systems, such as the post asphyxia score (PAS) (**Lipper et al., 1986) ,** the neonatal behavioural neurological assessment **(Bao et al., 1993) ,** the Sarnat and Sarnat grading system **(Sarnat, 1976)** and the Thompson score. Problems with these scoring systems include difficulties in reliably measuring some clinical parameters soon after birth (e.g. assessing primitive reflexes, breathing, and seizures in sedated or paralysed ventilated infants) and the occurrence of intermediate signs that do not fit the defined classifications. The level of HIE may change over the first few days after birth and is affected by medication and biochemical abnormalities. Several studies carried out before, indicated that aEEG is an excellent early predictor of neurological outcomes following HIE. A recent systematic review reported that aEEG performed within 24 hours of birth has a sensitivity of 93% (95% confidence interval (85–97%) and specificity of 91% (95% confidence interval 67–98%). Furthermore, individual studies report a positive predictive value of more than 80% for predicting death or disability in infants with HIE. Combining the grade of clinically assessed encephalopathy with the grade of aEEG abnormality

further improves predictive accuracy **(Van et al., 2013).**

HIE scoring systems have been used in various studies. Portman et al **(Portman et al., 1990)** developed a score that predicts early morbidity and mortality. While others have developed a score that has been related with long-term outcome **(Lipper et al., 1986).** Most recently , Miller and collaborators from the University of California at San Francisco validated a simple scoring system based on the typical signs and symptoms of NE.The maximum score from the first 3 days of life is used for prognostication **(Miller et at., 2008).**

Table 1. Miller system **(Miller et al., 2008)**

Signs and Symptoms	Score=0	Score=1
Feeding	Normal	Gavage feeding,gastrostomy tube,or feeding by mouth not tolerated
Alertness	Alert	Irritable, poorly responsive,or comatose
Tone	Normal	Hypotonia or hypertonia
Respiratory status	Normal	Respiratory distress(need for CPAP or M.V)
Reflexes	Normal	Hypereflexia, hyporeflexia,or absent reflexes
Seizures	Normal	Suspected or confirmed clinical seizures

The most widely used classification of HIE is that of Sarnat and Sarnat which groups affected infants into one of three categories: mild, moderate and severe which correlate with the descriptions of stage 1,2 ,3. The decision as to whether an infant falls into the moderate or severe category is at times difficult and the outcome of infants in the moderate group is variable. It utilizes the EEG and other laboratory parameters that may not be available in a neonatal unit in the developing countries.

Application of this grading system is also time consuming and requires some paediatric expertise **(Sarnat, 1976)**.

Table 2. Sarnat score **(Sarnat, 1976)**

	Stage 1	Stage 2	Stage 3
Level of Consciousness	Hyperalert	Lethargic or obtund	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent Decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental Myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high Threshold	Absent
Oculo- vestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalised Sympathetic	Generalised Parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable

Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal Motility	Normal or decreased	Increased, diarrhea	Variable
Other			
Seizures	None	Common, focal or Multifocal	Uncommon (excluding decerebration)
Electroencephalo-gram findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-to 1½- Hz spike-and-wave	Early: periodic pattern with isopotential phases Later: totally isopotential
Duration	Less than 24 hours	2–14 days	Hours to weeks

Fenichel modified this score to a score depend on clinical symptoms which distinguishes a mild , moderate and severe encephalopathy which could be linked to later neurodevelopmental outcome **(Fenichel, 1983).**

Table 3. Fenichel score **(Fenichel, 1983)**

Symptoms	Mild	Moderate	Severe
Consciousness	Irritable /Hyperalert	Lethargic	Comatosed
Tone	Mild abnormal	Moderately abnormal	Severly abnormal
Suck reflex	Abnormal	Poor	Absent

Primitive reflexes	Exaggerated	Depressed	Absent
Seizures	Absent	Present	Present
Brain stem reflexes	Normal	Normal	Impaired
Respiration	Tachypnea	Occasional apnea	Severe apnea

Our study use the modified Sarnat scoring which has been validated by Thompson et al. and has more clinical approach, with numeric value, and fewer items. It contains many of the features included in the three stages of Sarnat and Sarnat but excludes autonomic function, the deep reflexes and some of the primitive reflexes. He have added the grasp reflex, the respiratory pattern and a clinical assessment of the fontanelle tension since ultrasound is not generally available in developing countries The Thompson score is a numeric scoring system that requires no equipment and no specific training with a high predictive value for outcome. For clinicians working in areas where sophisticated technology is unavailable, this scoring system will be very useful **(Thompson et al., 1997)**.

Recently, Thompson scores were analyzed during or just before the start of hypothermia **(Horn et al., 2013).** This study is therefore assessing the HIE score in our set-up to devise a means of predicting early neurodevelopment outcome in babies with birth asphyxia.

Thompson Score :

The score consists of a clinical assessment of nine signs.

Table 4. Thompson score **(Thompson et al., 1997)**

Sign	**0**	**1**	**2**	**3**
Tone	Normal	Hypertonia	Hypotonia	Flaccid
LOC	Normal	Hyperalert Stare	Lethargic	Comatose
Fits	None	Infrequent <3 day	Frequent >2 day	
Position	Normal	Fisting Cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suckling	Normal	Poor	Absent	
Respiration	Normal	Hyperventilation	Brief apnea	Apnea IPPV
Fontanell	Normal	Full not tense	Tense	

Tone:

The tone progresses from normal and slightly increased peripheral tone in the mildly affected infant to the more severely affected infant who is generally hypotonic or completely flaccid **(Thompson et al., 1997).**

LOC (level of consciousness)

The assessment of LOC is as described originally by Sarnat and Samat . The mildly affected infant has a normal LOC or is hyperalert and staring with normal or decreased spontaneous movement and exaggerated responses to minimal stimuli. The more severely affected infant progresses through lethargy to complete unresponsiveness "stuporose",as described by Sarnat **(Thompson et al., 1997).**

Fits (clinically apparent seizures)

The score increases with increasing frequency of seizures **(Thompson et al., 1997).**

Position

This is assessed again as described by Samat and Sarnat but in this study an intermediate score of 1 is given to the infant who has mild to moderate HIE and who shows intermittent bicycling movements of the limbs together with fisting (thumbs flexed. adducted and opposed across the palms) **(Thompson et al., 1997).**

Primitive reflexes

These reflexes are normal in the mildly affected infant, poor or partial in moderate HIE and absent in severe HIE **(Thompson et al., 1997).**

Respiration

In mild HIE the infant breathes normally or hyperventilates More severely affected infants have episodes of apnoea and may require ventilation **(Thompson et al., 1997).**

Fontanelle tension

The more severely affected infant may have a full or tense (bulging) fontanelle **(Thompson et al., 1997).**

Each sign is scored from 0 to 3 and the score for each day is totalled. The higher the score the more severely affected the infant. Score 0 is considered normal. The maximum possible score on any one day is 22. Infants with score (1–10) are considered to have mild HIE, (11–14) have moderate HIE and (15–22) are considered to have severe HIE. The score

is equally applicable in a ventilated infant. It cannot be applied in a paralysed infant **(Thompson et al., 1997).**

Thompson score was evaluated in many studies.first study was introduced by Thompson et al at 1997, who assessd the value of the score in predicting neurodevelopmental outcome at 1 year of age. Forty-five term infants enrolled into the study. infants were evaluated at at 18 weeks of age and at 12 months of age by full neurological examination and the Griffiths Scales of Mental Development. Five infants were assessed at an earlier stage, four who died before 6 months of age and one infant who was hospitalized at the time of the 12 month assessment. Twenty-three (58%) of the infants were normal and 17 (42%) were abnormal, 16 with cerebral palsy and one with developmental delay. five infants were lost to follow-up. The hypoxic ischaemic encephalopathy score was highly predictive for outcome. The best correlation with outcome was the peak score; a peak score of 15 or higher had a positive predictive value of 92% and a negative predictive value of 82% for abnormal outcome, with a sensitivity and specificity of 71% and 96%, respectively **(Thompson et al., 1997).**

Patients and Methods

Study population :

This study was a prospective cross-sectional study conducted in Neonatal Intensive Care Unit, Department of Pediatrics, Benha University Hospitals and Ahmed Maher Teaching Hospital from April 2018 to December 2018 . A total of (50) post asphyxiated term neonates born in labor room/obstetric operation theatre were recruited. An informed consent was taken from all the parents. The protocol was approved by the institutional ethical committee of Benha University Hospitals. Subjects included in this study under the following inclusion and exclusion criteria.

Inclusion Criteria :

- Full-term, asphyxiated babies (5 minute Apgar Score ≤ 7).
- Both sex.

Exclusion Criteria:

- Respiratory depression due to intracranial bleeding.
- Neonates with major congenital malformations of CVS, CNS, Respiratory system.
- Dysmorphic Babies.
- Severe hyperbilirubinemia bordering on kernicterus.
- Cases with hypoglycemia or meningitis as cause of encephalopathy.

The standard for defining an intrapartum hypoxic-ischemic event as sufficient to produce moderate to severe neonatal encephalopathy which subsequently leads to cerebral palsy has been established according to American Academy Of Pediatrics and the American College of Obstetricians and Gynecologists include the following:

- Profound metabolic or mixed acidemia (pH< 7.00) in umbilical cord blood.
- Persistence of low Apgar scores less than 3 for more than 5 minutes.
- Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities) .
- Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine)

Asphyxia or brain hypoxia may also less commonly occur remote from the time of delivery and therefore clinical criteria and symptoms may not meet all of the criteria set forth by the AAP and ACOG **(AAP, 2003).**

Methods

All cases is subjected to:

- An informed oral consent was obtained from all parents before involving them in the study as no interventional process was done and there was no perceived risk.
- For delivery room resuscitation, the standard Neonatal Resuscitation Program of American Academy of Pediatrics guidelines is followed.

- Full History taking:

- **A-prenatal** : to detect risk factor for perinatal asphyxia:

1. Pre-eclampsia.
2. Maternal age .
3. General anesthesia.
4. Meconium Aspiration.
5. Chorioamnionitis.
6. Maternal diabetes.
7. Maternal drugs intake.

- **B-Natal:**

1. Place and Mode of delivery.
2. Apgar score at 1 and 5 minutes **(Apgar, 1953).**

- Assesment of gestational age through analysis of last menstrual date and Ballard Score **(Ballard et al., 1991).**

- Physical examination:

1. General examination:

- Vital signs.
- Regional examination (Head and Neck, spine, Back and Genitalia).
- Neonatal Reflexes (Moro, Grasp, Suckling).
- Anthropometric measurement including weight, height and head circumference.

2. Systemic examination:

- Chest examination.
- Heart examination.
- Abdominal examination.
- Neurological examination (Conscious state, Muscle Tone, Muscle Power, Reflexes, Primitive reflexes, Cranial nerves as possible).
- Staging system : HIE was defined as mild , moderate ,and severe using Sarnat staging system **(Sarnat, 1976).**
- Serial Thompson score at day 1,3,7 as shown in Table (1). The Thompson score was performed by the neonatologists in the unit.

Table 1. Thompson Score **(Thompson et al., 1997)**

S	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
Loc	Normal	Hyper alert	Lethargic	Comatose
Fits	None	<3/day	>2/day	
Posture	Normal	Fisting/Cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent	
Respiration	Normal	Hyperventilation	Brief Apnea	IPPV(apnea)
Fontanel	Normal	Full not Tense	Tense	

Infants with score (1–10) are considered to have mild HIE, (11–14) have moderate HIE and (15–22) are considered to have severe HIE.

- **Investigation:**

Labatory testing was for all subjects and included:

❖ Cord blood gas analysis was done at birth (pH, pCO2, bicarbonate, base deficit). cord blood samples were collected from double clamped umbilical cord, anaerobically, using heparinized disposable syringes (2ml syringe washed by 1000IU/ ml heparin). It directly measures pH, pCO2, bicarbonate, base deficit.

❖ Routine investigation:

1. Complete blood count.
2. C-reactive protein.
3. Renal function (urea, creatinine) . AKI should be suspected if the serum creatinine concentration is increased >1.0 to 1.5 mg/dL **(Durkan and Alexander, 2011).**
4. Prothrombin time, Partial thromboplastin time, International normalized ratio. (Coagulopathy should be suspected if PT > 16 ±1.4 , PTT > 42.9 ±5.8) **(Andrew et al., 2000).**
5. Serum Transaminases (ALT > 50 U/L and AST > 150 U/L) **(Wu, 2006).**
6. Serum electrolytes.

❖ Radiological investigation:

- ✓ Plain chest X-ray to all cases.
- ✓ Cranial U/S to all cases.
- ✓ CT on brain if indicated.
- ✓ MRI if possible.
- ✓ ECHO was done in the presence of a clinical indication.

- All cases were followed up until discharge to asses outcome.

- After follow up, the studied cases were grouped into three subgroups:
  - ✓ Group who died .
  - ✓ Group who were neurologically affected .
  - ✓ Group with normal outcome.

Statistical methods

Data management and statistical analysis were done using SPSS vs.25. Numerical data was summarized as means and standard deviations or medians and ranges. Categorical data was summarized as numbers and percentages. Comparisons between survivors and non survivors were done using Mann Whitney U test for numerical variables. Categorical variables were compared using Chi-square test or Fisher exact test if appropriate. Apgar score 1 minute and 5 minutes were compared using Wilcoxon signed ranks test. Thompson scores at 1, 3 and 7 days were compared using Friedman's test. Correlation analysis was done using Spearman's correlation. "r" is the correlation coefficient. It ranges from -1 to +1. -1 indicates strong negative correlation. +1 indicates strong positive correlation while 0 indicates no correlation. ROC analysis was done for Thompson score at day 1 for prediction of mortality, Area Under Curve with 95% confidence interval and diagnostic indices including sensitivity, specificity were calculated. Multivariate logistic regression analysis was done for prediction of mortality, Odds ratios with 95% confidence intervals were calculated. All P values were two sided. P values less than 0.05 were considered significant **(Peacock et al., 2011).**

Results

This study was conducted in Neonatal Intensive Care Unit, department of Pediatrics, Benha University Hospitals and Ahmed Maher Teaching Hospital on 50 post asphyxiated term neonates.

➢ Neonatal characteristics

Table (1) Neonatal characteristics of the whole study group

		N	%
Gender	**Males**	28	56.0
	Females	22	44.0
Mode of delivery	**CS**	33	66.0
	Vaginal delivery	17	34.0

Table (2) Neonatal demographic data of the whole study group

Gestational Age(wks)	**Mean (Range)**	38.32 wks (37-40)
Birth Weight(gm)	**Mean ±SD**	3.260 gm (± 0.625)

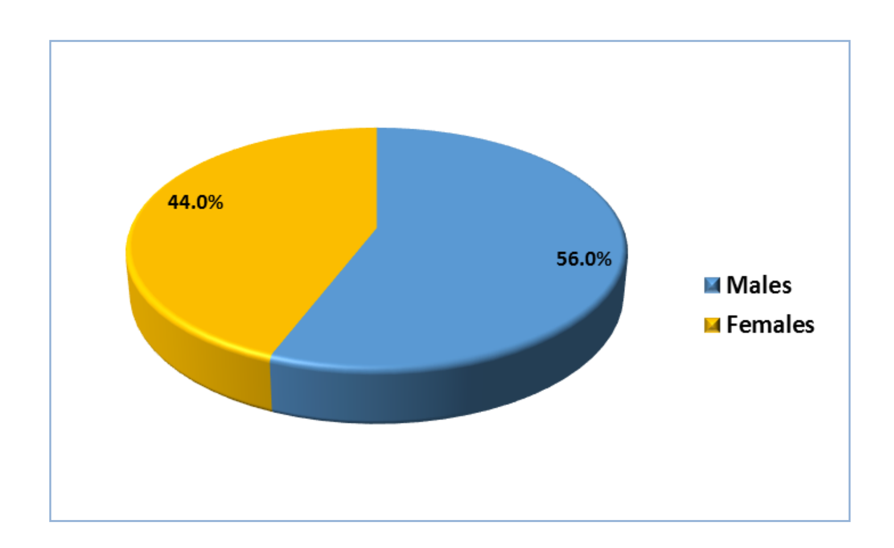


Figure (1):Sex distribution among cases

- Table 1 shows that male were predominant in our study represent 56% of neonates while 44% were females. The most frequent mode of delivery was Cesarean section (66.0%). Vaginal delivery represented 34%. ***(Table(1)& Figure(1)).***
- Table 2 shows that mean gestational age was 38.32 wks ,and median birth weight 3.260 gm.

➢ Maternal characteristics

Table (3) Maternal characteristics of the whole study group

		Mean ±SD
Maternal age(years)		30 ±5
Parity	Nultipara	10 (20.0)
	Mullipara	40 (80.0)
PROM	Yes n (%)	6 (12.0)
Consanguinity	Yes n (%)	3 (6.0)

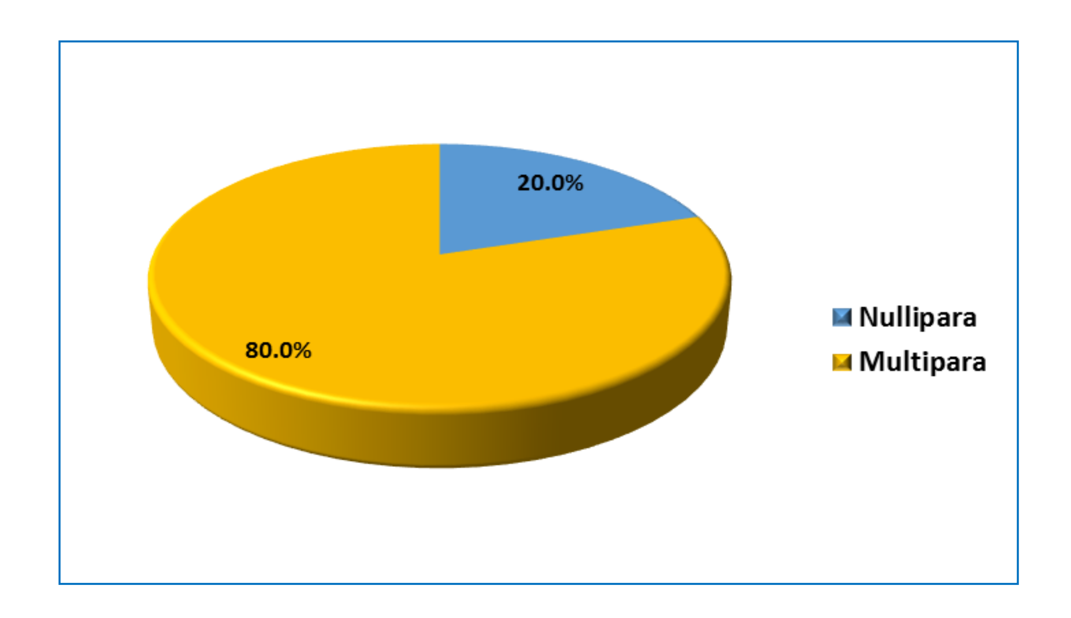


Figure (2):Maternal Parity distribution cases

❖ Table 3 shows that Mean maternal age was 30 years with standard deviation of ±5. 40% of mothers were multipara. PROM was noticed in only 12.0%. 6% showed positive consanguinity. ***(Table(3) and Figure(2))***

➢ Maternal co-morbidity

Table (4):Frequency distribution of maternal co-morbidities

	N	%
Obstructed labour	11	22
Gestational Diabetes	5	10.0
Accidental Hage	2	4.0
Epilepsy	2	4.0
Rupture Uterus	4	8.0
Preeclampsia	4	8.0
Severe Anemia	2	4.0
Placenta Previa	4	8.0

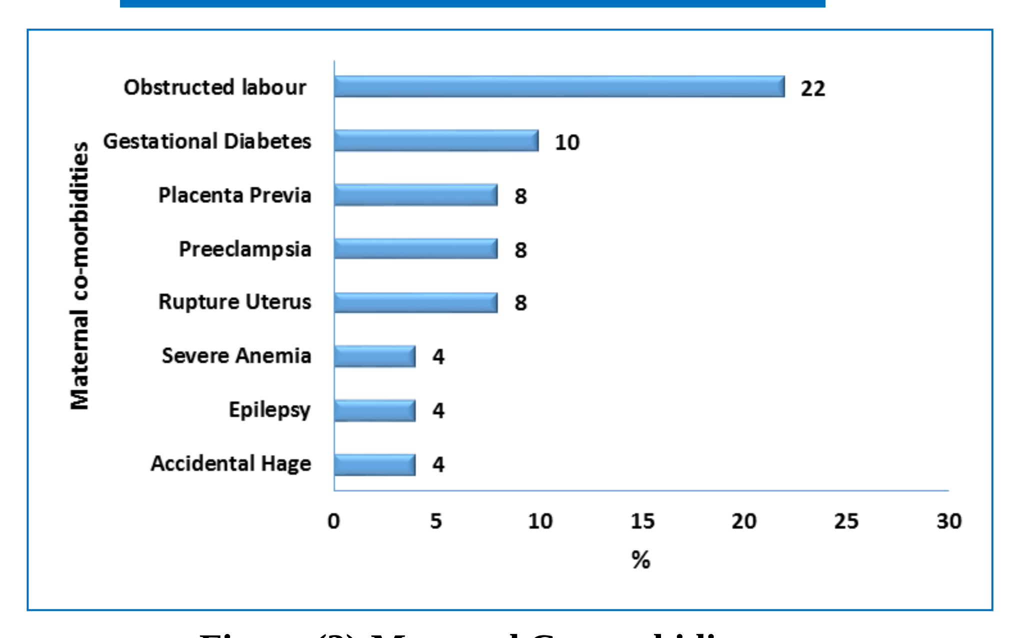


Figure (3):Maternal Co-morbidity

❖ Obstructed labour was observed on 22% of cases .Gestational diabetes was a co-morbidity in 10% of mothers. 8% of mothers experienced rupture uterus. Pre-eclampsia was found also in 8% of mothers. Epilepsy, accidental hemorrhage and anemia represented 4% for each. ***(Table(4) and figure (3))***

➢ Apgar SCORE at 1 minute and 5 minutes

Table (5):Apgar score at one and five minutes

	Median	Range	P value
Apgar 1 min	3	(0 - 5)	<0.001
Apgar 5 minutes	5	(1 - 7)	

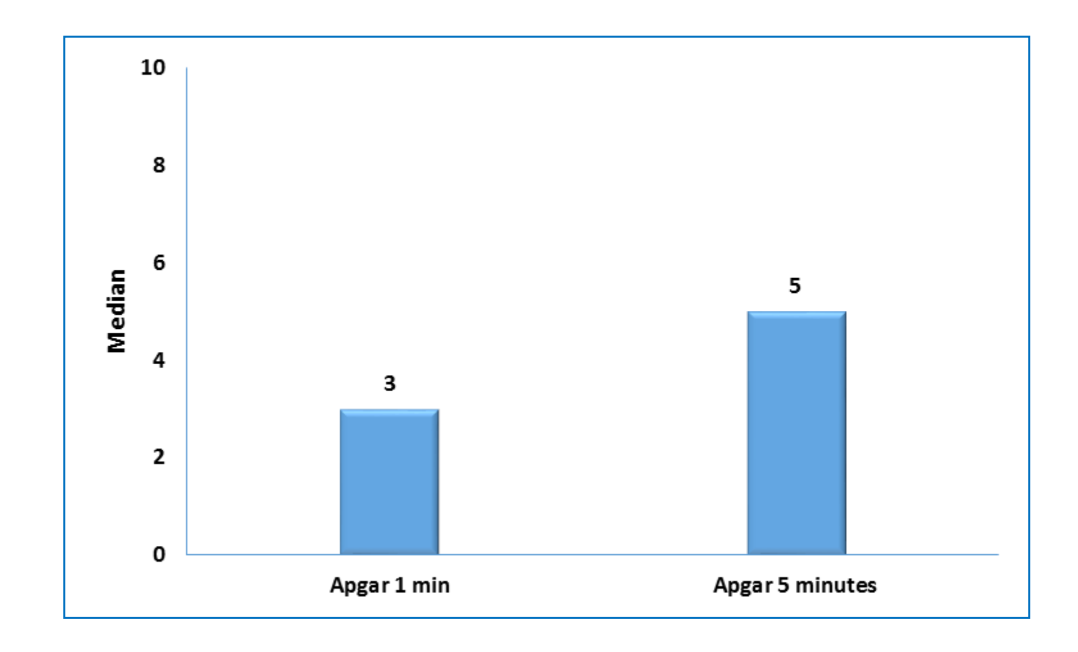


Figure (4):Median Apgar score in the whole study group

- ❖ Median Apgar score at 5 minutes was higher (5) than that at 1 minute (3). This difference was statistically significant (P value <0.001). ***(Table(5)& Figure(4))***

Blood gases

Table (6):Blood gases in the whole study group

PH	**Mean ±SD**	7.12 ±0.24
PCo2(mm.Hg)	**Median (range)**	40.6 (15.1 - 114)
HCo_3(mEq/litre)	**Mean ±SD**	14.1 ±4.2
BE(mmol/litre)	**Median (range)**	-11.7 (-32 - 25)

- Mean PH was 7.12 with standard deviation ±0.24. Median PCO2 was 40.6 and ranged from 15.1 to 114. Mean HCO3 was 14.1 with standard deviation ±4.2. Median Base excess was -11.7 and ranged from -32 to 25. ***(Table(6)***

➢ Seizures and sarnat score

Table (7): Seizures and Sarnat staging in the whole study group

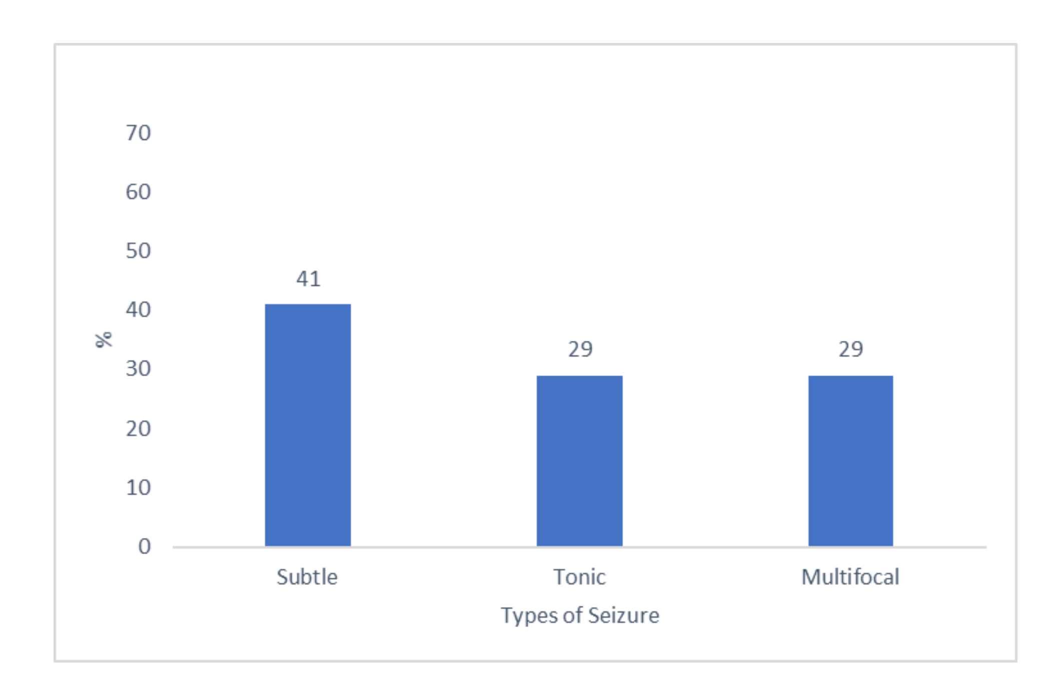
		N	%
Seizures	Yes	24	48.0
Sarnat staging N=50	stage 1 (N=11)	0	0.0
	stage 2 (N=26)	15	62.0
	stage 3 (N=13)	9	37.0

Figure (5): Distribution of cases as regard Sarnat score

❖ Seizures was experienced in 48% of patients. As regard Sarnat staging, majority of patients were stage 2 (62%). Followed by stage III which represented 37%. ***(Table(7) and figure(5))***

Table (8): Types of seizures

Types of seizures	Subtle	Tonic	Multifocal	Total
N=24 (%)	N(%)	N (%)	N(%)	
	10(41%)	7(29%)	7(29%)	24(100%)



Figure(6):Distribution of seizure among cases

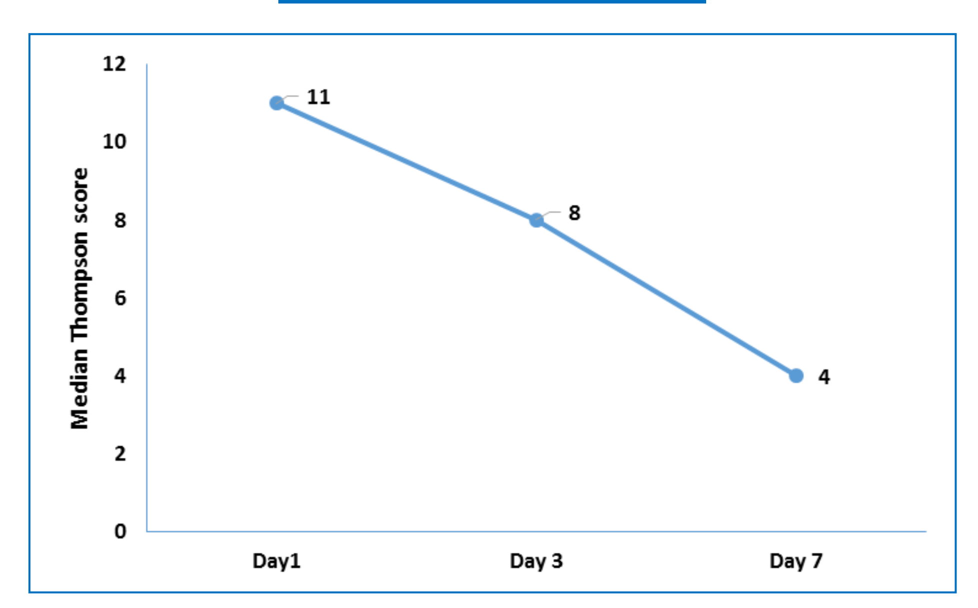
- 41% of patient experienced subtle convulsion in the form of smacking .suckling , blinking while 29% experienced tonic convulsion, 29% of patient had multifocal convulsion***(Table(8) & Figure(6))***

➢ Thompson score at day 1, 3 and 7

Table (9):Thompson score at day one, three and seven

		Median	Range	P value
Thompson score	Day1	11	(6 - 20)	<0.001
	Day 3	8	(0 - 19)	
	Day 7	4	(0 - 18)	

Pair	P value
Day 1 vs. Day 3	<0.001
Day 1 vs. Day 7	<0.001
Day 3 vs. Day 7	<0.001



Figure(7):Serial improvement of median Thompson score

❖ Thompson score showed an overall significance between day 1, day 3 and day 7 as follows:

- Median Thompson score was higher in day 1 (11) than day 3 (8). This difference was statistically significant (P value <0.001).
- Median Thompson score was higher in day 1 (11) than day 7 (4). This difference was statistically significant (P value <0.001).

- Median Thompson score was higher in day 3 (8) than day 7 (4). This difference was statistically significant (P value <0.001). ***(Table(9)& Figure(7)***

➢ Complications

Table (10):Frequency distribution of complications

	N	%
Resp. Affection	34	68.0
Renal Affection	24	48.0
Hepatic Affection	23	46.0
Coagulopathy	22	44.0
Sepsis	15	30.0

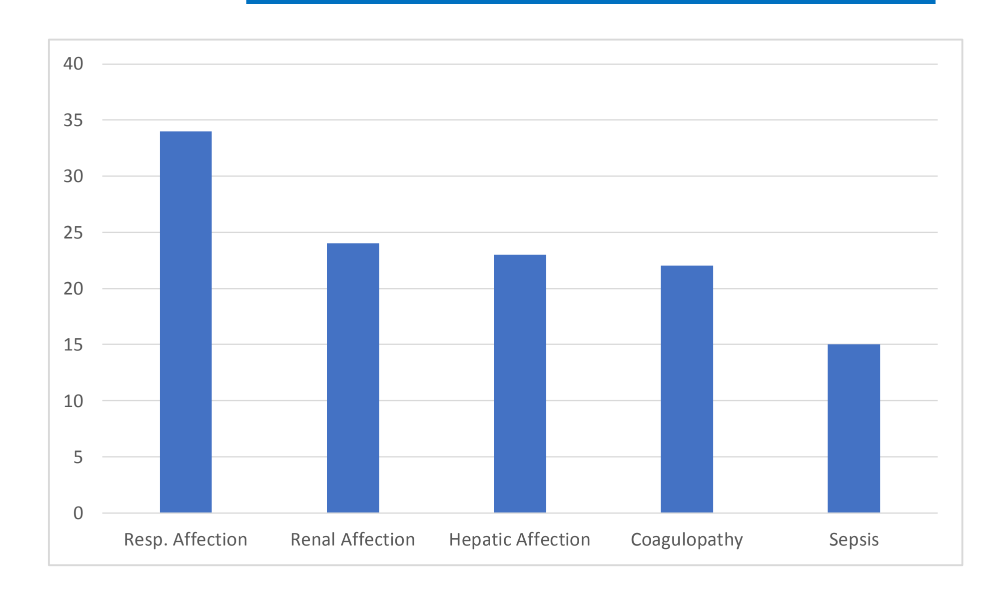


Figure (8):Distribution of complication in the whole study group

❖ 68% of patients had respiratory complication in the form of respiratory distress need M.V , pneumonia. Renal affection (AKI should be suspected if the serum creatinine concentration is increased (>1.0 to

1.5 mg/Dl) and hepatic affections (serum transaminases >42 mg/dl) were found in 48% and 46% of neonates respectively. 44% of neonates had coagulopathy(PT > 13 ±1.4 , PTT > 42.9 ±5.8) and 30% experienced sepsis while admitted at NICU. ***(Table(10)&Figure(8))***

➢ Radiological findings

Table (11) Frequency distribution of radiological findings

	N	%
Brain affection by US(N=50)	26	52.0
Brain Affection by CT(N=11)	4	36.4
Brain Affection by MRI (N=3)	2	66.7
ECHO Affected (N=23)	16	69.6

Only 11 patients did CT brain. Only 3 patients did MRI.
Only 23 patients did ECHO

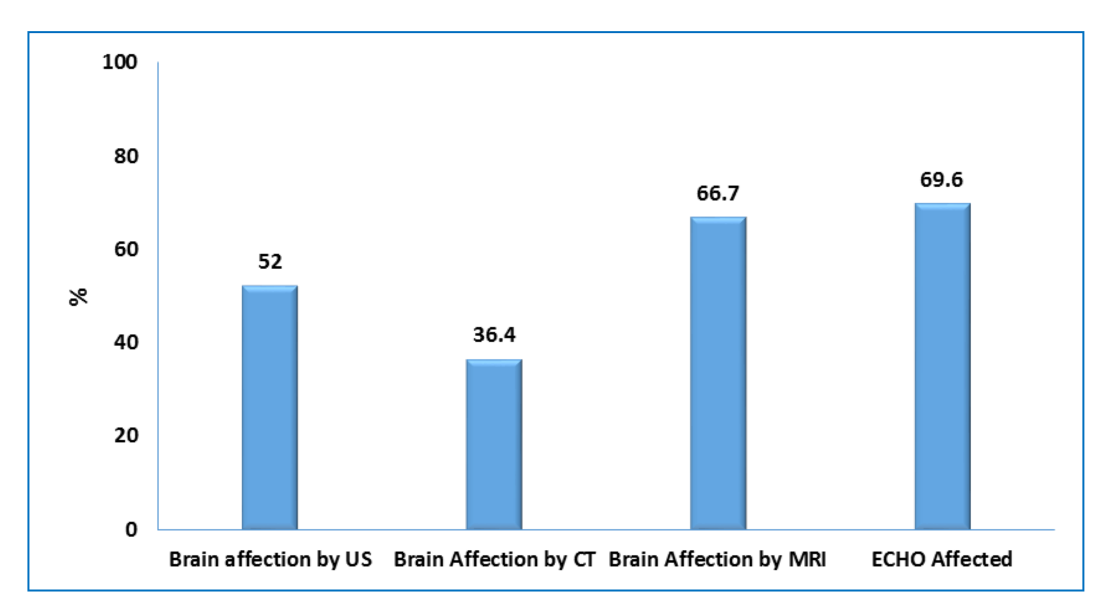


Figure (9): Positive Radiological finding in the whole study group

- Our study shows brain affection in Cranial US in 52% of neonates in the form of:
    - cerebral oedema **9 cases** .
    - decrease resistive index less than 0.7 was in **15 cases**.
    - dilatation of ventricles later on discharge **2 cases.**
    - echogenicity in thalami **2 cases**.
- CT brain showed brain affection in **36.4%** of neonates underwent CT **(11 neonates only underwent CT**) in the form of dilatation of ventricles and cerebral oedema.
- Only 3 patients did MRI brain. **Two of them** showed brain affection (in the form of abnormal signals of posterior limb of internl capsule in T1,abnormality of basal ganglion).
- ECHO was performed on 23 neonates, **16 of them** showed cardiac affection in the form of :
    - pulmonary hypertension **(14 cases)** .
    - decrease ejection fraction and myocardial contractility **(2 cases).**

(Table(11) &Figure(9)

➢ Outcome

Table (12):Frequency distribution of different outcome

		N	%
Outcome	Discharge	22	44.0
	Morbidity	8	16.0
	Mortality	20	40.0

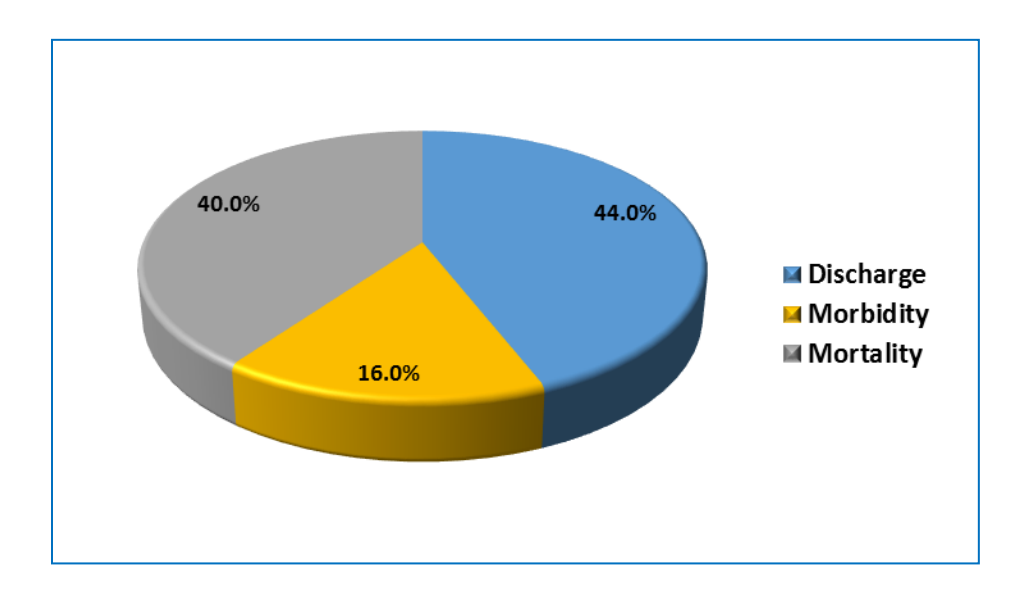
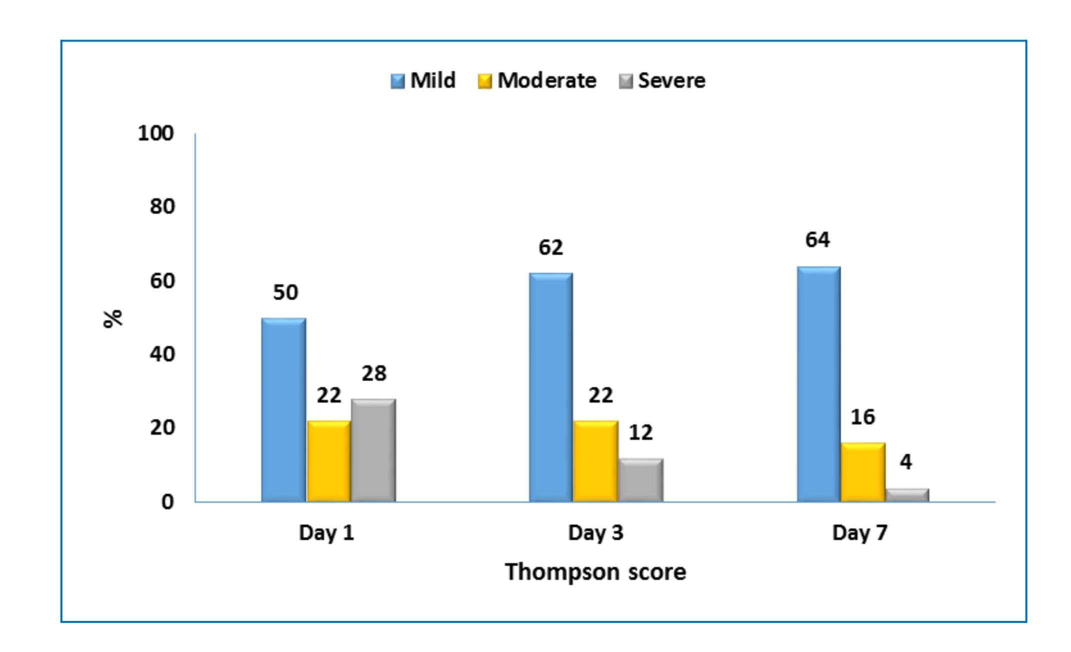


Figure (10):Outcome of the whole study group

- ❖ Outcome measures were grouped as normal or abnormal with morbidity (convulsions, abnormal muscle tone or reflexes, feeding difficulty and abnormal radiological finding) or death(mortality).
- ❖ Mortality and morbidity represented 40% and 16% of neonates respectively. 44% of neonates were discharged neurologically normal. ***(Table(12)& Figure(10))***

Table (13):Evaluation and grading of Thompson score at day 1,3,7

Thompson score	Day 1 (n = 50)	Day 3 (n = 50)	Day 7 (n = 50)
Mild	25 (50.0)	31 (62.0)	32 (64.0)
Moderate	11 (22.0)	11 (22.0)	8 (16.0)
Severe	14 (28.0)	6 (12.0)	2 (4.0)



Figure(11):Distribution of cases as regard Thompson score

- In our study , mild Thompson score on day 1,3,7 was 25 (50%) , 31(62%), 32(64%) respectively , moderate Thompson score on day 1,3,7 was 11(22%) ,11(22%), 8(16%) respectively and severe Thompson score on day 1,3,7 was 14(28%),6(12%), 2(4%), There was clinical improvement among HIE patients as indicated by serial Thompson score done on day 1, 3 and 7***(Table(13) &Figure(11)).***

➢ Neonatal characteristics in survivor and non-survivor neonates

Table(14):Neonatal characteristics in survivor and non-survivor neonates

		Mortality				P value
		Yes (n = 20)		No (n = 30)		
		N	%	N	%	
Gender	**Males**	9	45.0	19	63.3	0.201
	Females	11	55.0	11	36.7	
Mode of delivery	**CS**	15	75.0	18	60.0	0.273
	Vaginal delivery	5	25.0	12	40.0	

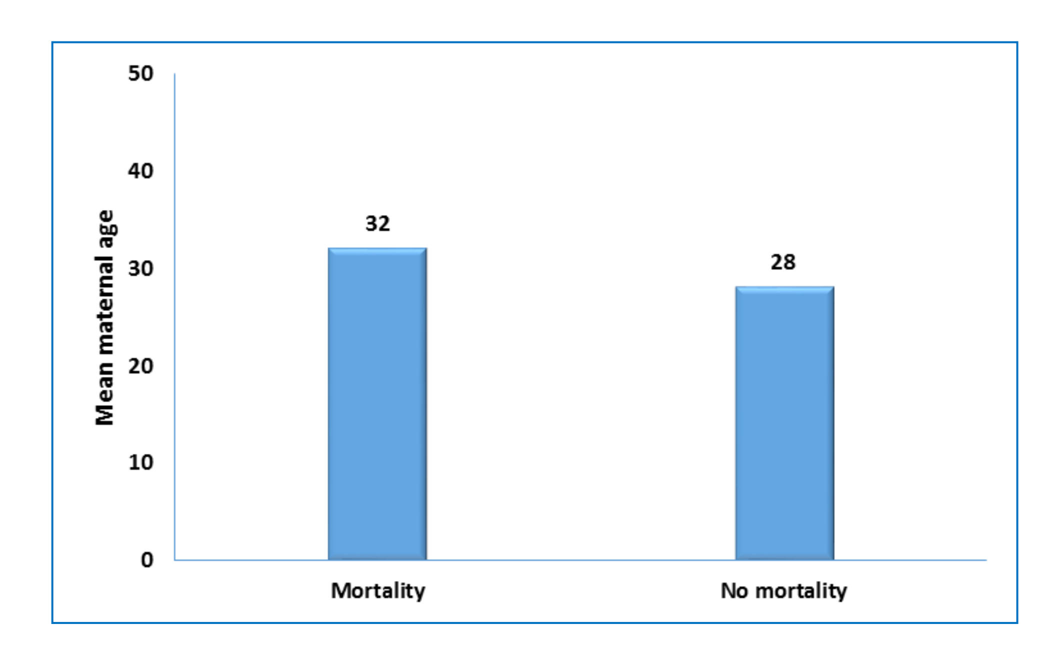
CS = Cesarean section

❖ There were no significant differences between survivor and non-survivor neonates as regard gender and mode of delivery. ***(Table(14))***

➢ Maternal characteristics in survivor and non-survivor neonates

Table(15):Maternal characteristics in survivor and non-survivor neonates

		Mortality		P value
		Yes (n = 20)	No (n = 30)	
Maternal age (years)	**Mean ±SD**	32 ±5	28 ±5	0.021
Parity	**Nullipara n (%)**	3 (15.0)	7 (23.3)	0.47
	Multipara n (%)	17 (85.0)	23 (76.7)	
Consanguinity	**Yes n (%)**	1 (5.0)	2 (6.7)	1.0



Figure(12): Comparison between survivors and non -survivors as regard maternal age

❖ Mean maternal age was higher in non-survivors (32) than that of survivors (28). This difference was statistically significant. (P value = 0.021).

❖ There were no statistical significant differences between survivors and non-survivors as regard parity and consanguinity. ***(Table (15)& Figure(12))***

➢ Maternal co-morbidities in survivors and non-survivors neonates

Table (16) Maternal co-morbidities in survivor and non-survivor neonates

	Mortality				P value
	Yes (n = 20)		No (n = 30)		
	N	%	N	%	
Gestational Diabetes	3	15.0	2	6.7	0.377
Obstructed labor	4	20.0	7	23.3	0.78
PROM	3	15.0	3	10.0	0.672
Maternal drugs	3	15.0	5	16.7	1.0
Accidental Hage	0	0.0	2	6.7	0.51
Epilepsy	0	0.0	2	6.7	0.51
Rupture Uterus	4	20.0	0	0.0	0.021
Preeclampsia	2	10.0	2	6.7	1.0
Severe Anemia	0	0.0	2	6.7	0.51
Placenta Previa	2	10.0	2	6.7	1.0

PROM = Pre mature rupture of membrane

- ❖ Our study shows that Rupture uterus was higher (20.0%) in non-survivors than that in survivors (0.0%). This difference was statistically significant. (P value = 0.021).
- ❖ There were no significant differences between survivors and non survivors as regard gestational diabetes, PROM, Obstructed labour, maternal drugs in pregnancy(clexan,Tegretol ,Antibiotics) , accidental hemorrhage, epilepsy, preeclampsia, anemia and placenta-previa. ***(Table(16)).***

➢ Apgar score in survivors and non-survivors neonates

Table (17): Apgar 1 minute and 5 minutes in survivor and non-survivor neonates

	Mortality				P value
	Yes (n = 20)		No (n = 30)		
	Median	Range	Median	Range	
Apgar 1 min	2	(0 - 5)	3	(0 - 5)	0.440
Apgar 5 minutes	4	(1 - 7)	6	(2 - 7)	0.004

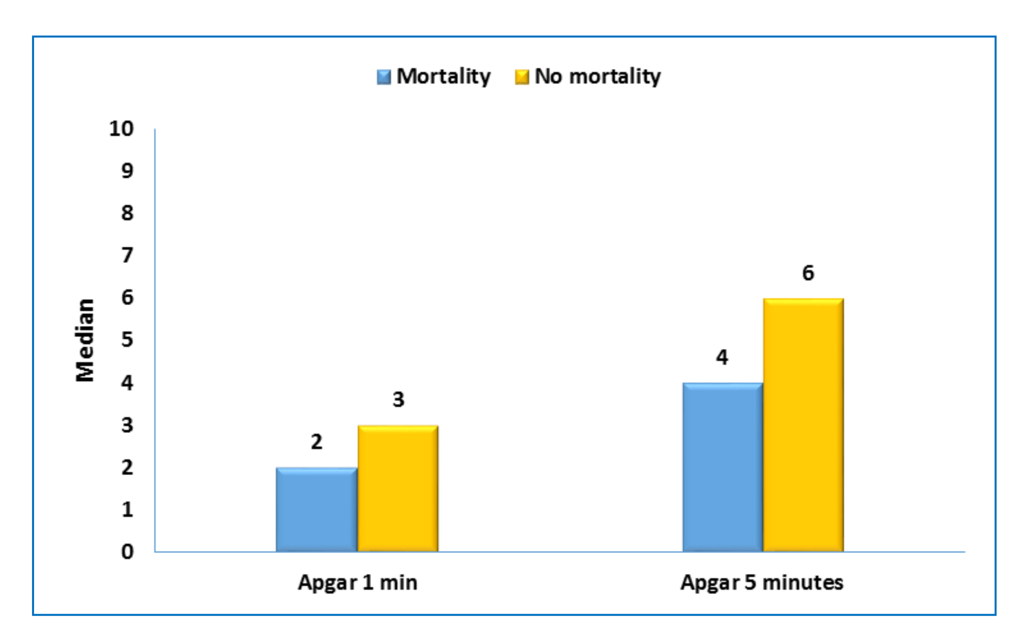


Figure (13):Comparison between mortality and morbidity regarding Apgar score

- ❖ Median Apgar score at 5 minutes was higher in survivors (6) than non-survivors (4). This difference was statistically significant (P value = 0.004)
- ❖ There was no significant difference in Apgar score at 1 minute between survivors and non survivors (P value = 0.440). ***(Table(17)&Figure(13))***

➢ Blood gases in survivor and non-survivor neonates

Table (18):Blood gases in survivors and non-survivors neonates

		Mortality		P value
		Yes (n = 20)	No (n = 30)	
PH	**Mean SD**	7.05 ±0.28	7.17 ±0.19	0.098
PCo_2(mm.Hg)	**Median (range)**	40 (23 - 110)	41.8 (15.1 - 114)	0.67
HCo_3(mEq/litre)	**Mean ±SD**	12.4 ±5	15.2 ±3.2	0.018
BE(mmol/litre)	**Median (range)**	-20 (-31 - 2.8)	-11 (-32 - 25)	0.067

BE = Base excess

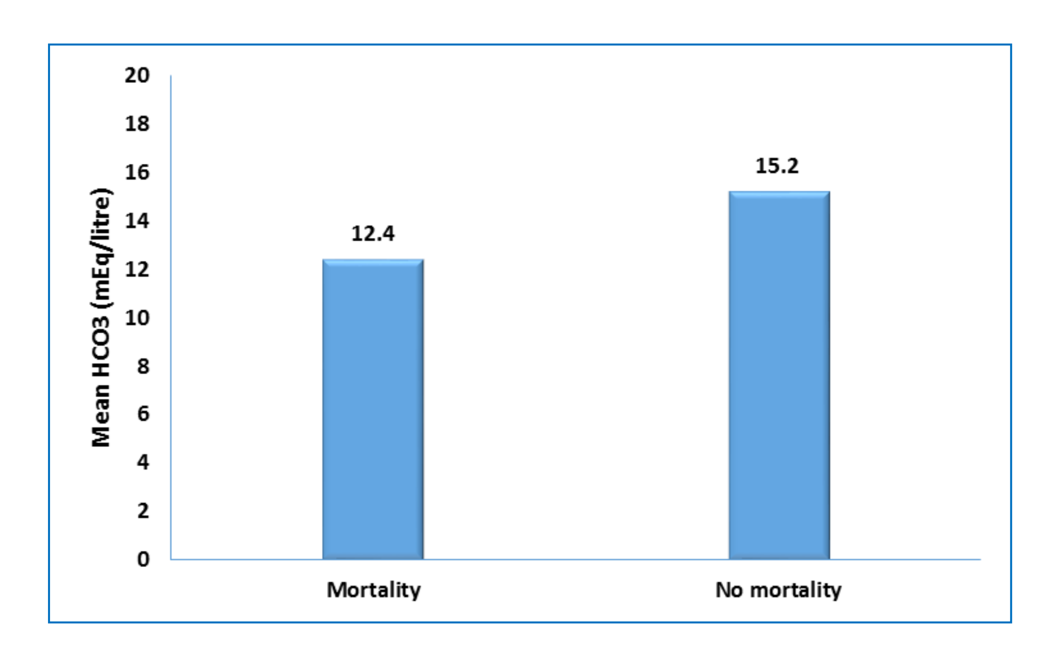


Figure (14):Comparison between survivors and non survivors regarding Hco_3

- Mean HCO_3 was higher in survivors (15.2) than that of non-survivors (12.4). This difference was statistically significant. (P value = 0.018).
- There were no significant difference between survivors and non-survivors as regard PH, PCO_2 and base excess. ***(Table(18)& Figure(14))***

➢ Seizures and Sarnat score in survivors and non-survivors neonates

Table (19): Seizures and Sarnat staging in survivors and non-survivors neonates

		Mortality				P value
		Yes (n = 20)		No (n = 30)		
		N	%	N	%	
Seizures	**Yes**	9	45.0	15	50.0	1.0
Sarnat staging	**stage1 N=11**	0	0.0	11	36.7	<0.001
	stage 2 N=26	8	40.0	18	60.0	
	stage 3 N=13	12	60.0	1	3.3	

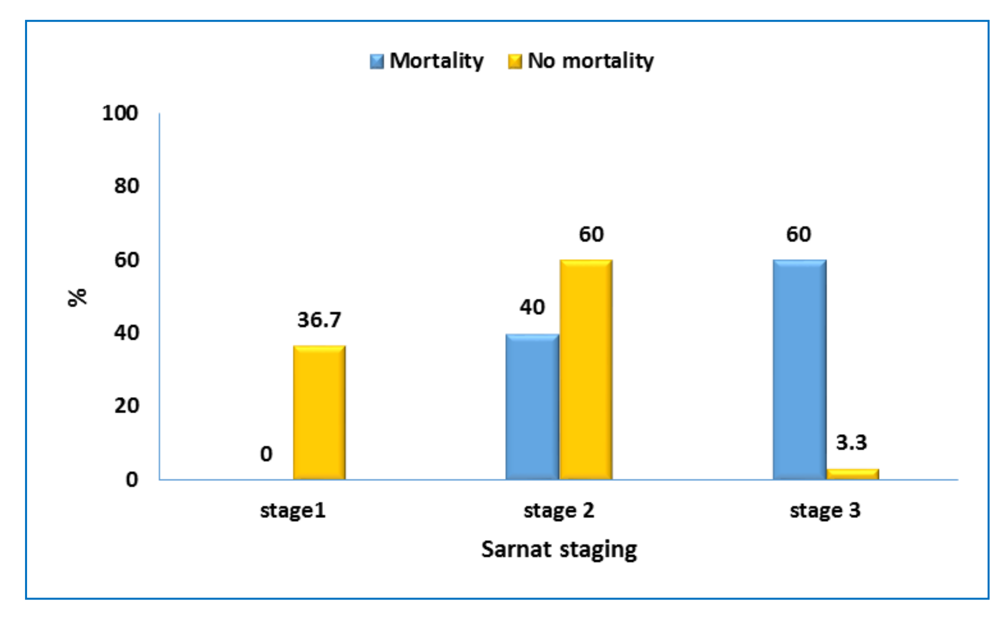


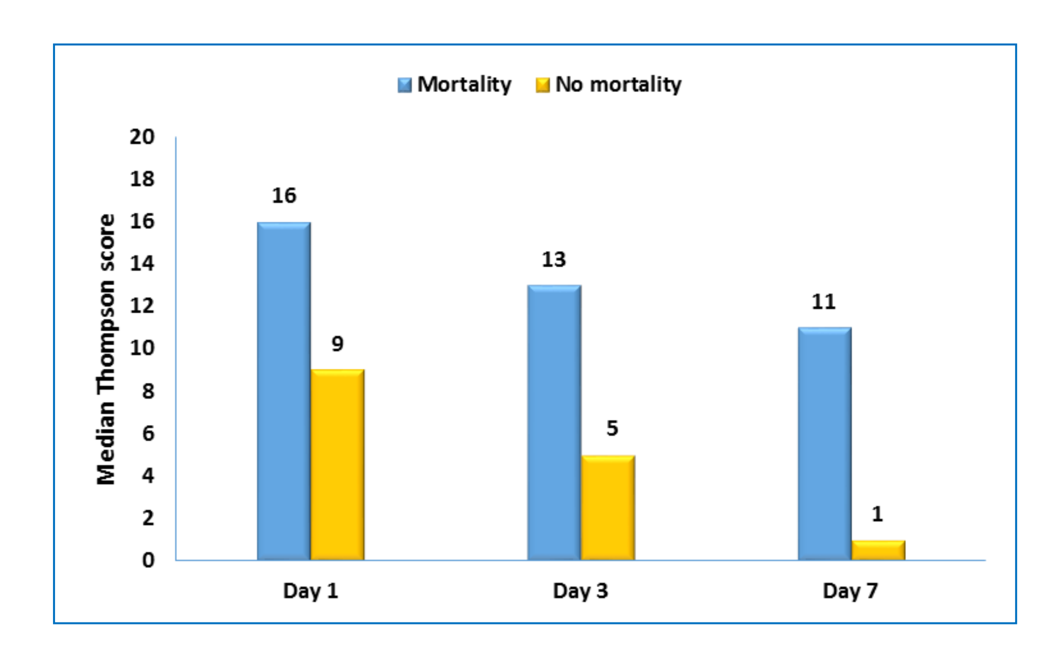
Figure (15): Sarnat staging in survivors and non-survivors

- ❖ Sarnat staging showed a significant difference between survivors and non-survivors. 36.7% of survivors were stage 1 compared to 0% of non-survivors. Also 60% of non-survivors were stage 3 compared to 3.3% in survivors.
- ❖ Seizures showed no significant difference between survivors and non-survivors. ***(Table(19)& Figure(15))***

➢ Thompson score in survivors and non-survivors neonates

Table (20):Thompson score at day 1, 3 and 7 in survivors and non-survivors

			Mortality		P value
			Yes (n = 20)	No (n = 30)	
Thompson score	Day 1	Median (range)	16 (9 - 20)	9 (6 - 15)	<0.001
	Day 3	Median (range)	13 (6 - 19)	5 (0 - 15)	<0.001
	Day 7	Median (range)	11 (1 - 18)	1 (0 - 11)	<0.001



Figure(16): Comparison between survivors and non-survivors as reguard median Thompson sore

❖ **At day 1**

- Median Thompson score was higher in non-survivors (16) than that of survivors (9). This difference was statistically significant. (P value <0.001).

❖ **At day 3**

- Median Thompson score was higher in non-survivors (13) than that of survivors (5). This difference was statistically significant. (P value <0.001).

❖ **At day 7**

- Median Thompson score was higher in non-survivors (11) than that of survivors (1). This difference was statistically significant. (P value <0.001). ***(Table(20)& Figure(16))***

➢ Complications in survivor and non-survivor neonates

Table (21): complications in survivors and non-survivors

	Mortality				P value
	Yes (n = 20)		No (n = 30)		
	N	%	N	%	
Resp.Affection	20	100.0	14	46.0	<0.001
Renal Affection	14	70.0	10	33.0	0.011
Hepatic Affection	12	60.0	11	36.0	0.105
Coagulopathy	14	70.0	8	26.0	0.002
Sepsis	6	30.0	9	30.0	1.0

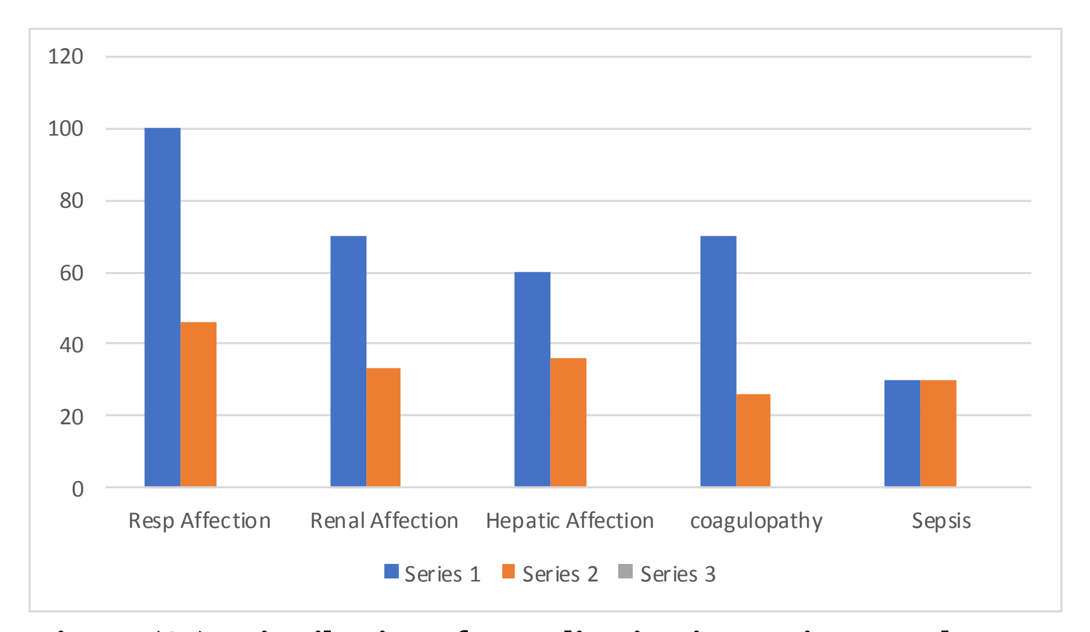


Figure (17): Distribution of complication in survivors and non-survivors

❖ Our study shows that Respiratory complication 100% ,renal affection 70% and Coagulopathy 70% was higher in non-survivors that that of survivors. This difference was statistically significant (P value = <0.001, 0.011 , 0.002 respictively).

❖ There were no significant difference between survivors and non-survivors as regard hepatic affection and sepsis. ***(Table(21)& Figure(17)***

➢ Brain US finding in survivor and non-survivor neonates

Table (22) Brain US finding in survivors and non-survivors

	Mortality				P value
	Yes (n = 20)		No (n = 30)		
	N	%	N	%	
Brain affection by US	11	55.0	15	50.0	0.729

US = Ultrasound

❖ There was no significant difference between survivors and non-survivors as regard brain affection detected by ultrasound. ***(Table(22))***

➢ ECHO findings in survivor and non-survivor neonates

Table (23) ECHO finding in survivors and non-survivors

	Mortality				P value
	Yes (n = 10)		No (n = 13)		
	N	%	N	%	
Cardiac affection	9	90.0	7	53.8	0.089

Only 23 patients did ECHO

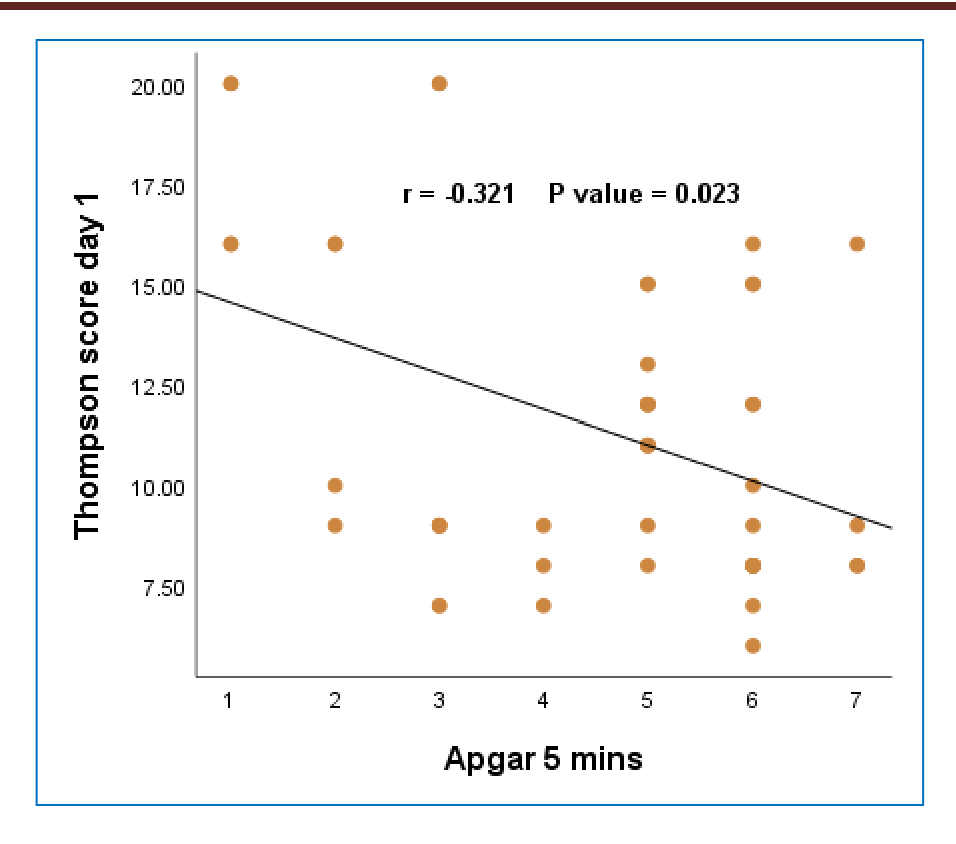
❖ There was no significant difference between survivors and non-survivors as regard cardiac affection by ECHO. ***(Table(23))***

➢ Thompson score correlation analysis with different parameters

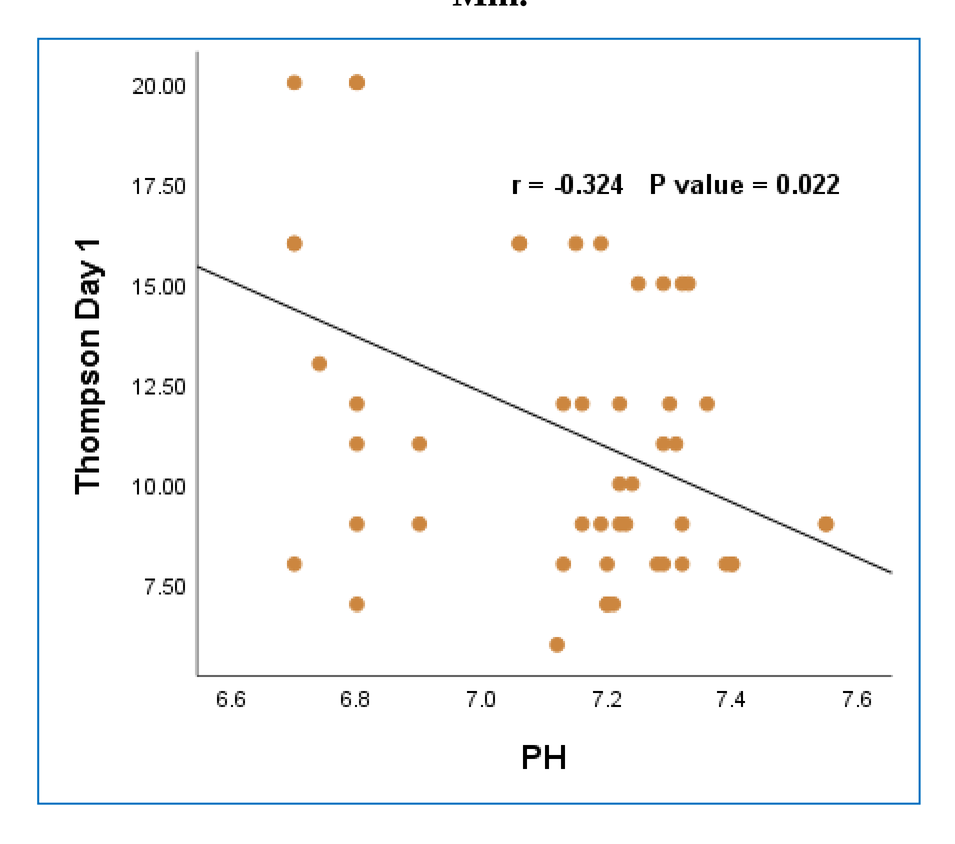
Table (24): Correlation analysis between Thompson score at day 1 and other study parameters

Thompson Day 1		
Hospital stay	R	-0.275
	P value	0.053
Maternal age(years)	R	0.032
	P value	0.826
Apgar 1 min	R	-0.205
	P value	0.153
Apgar 5 minutes	R	-.321*
	P value	0.023
Sarnat staging	R	0.851**
	P value	<0.001
PH	R	-.324*
	P value	0.022
PCo2(mm.Hg)	R	0.13
	P value	0.369
HCo3(mEq/litre)	R	-.414**
	P value	0.003
BE(mmol/litre)	R	-.374**
	P Value	0.007

BE = Base excess
***Significant**
****Highly significant**



Figure(18):Correlation between thompson score at D1 and Apgar 5 Min.



Figure(19):Correlation between Thompson score at D1 and PH

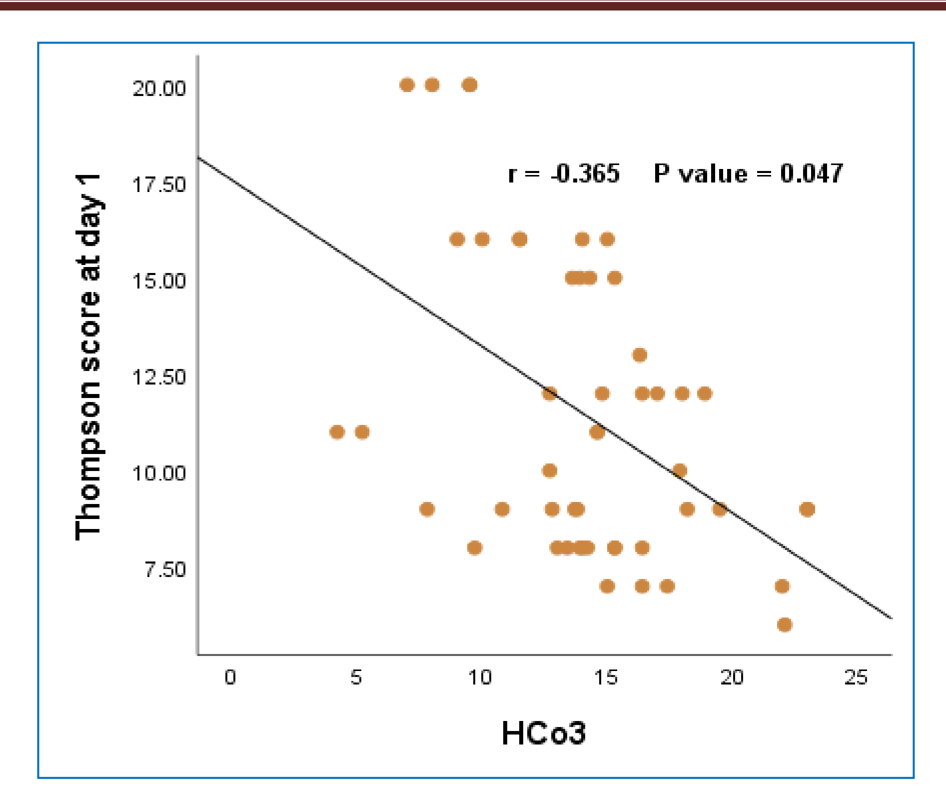
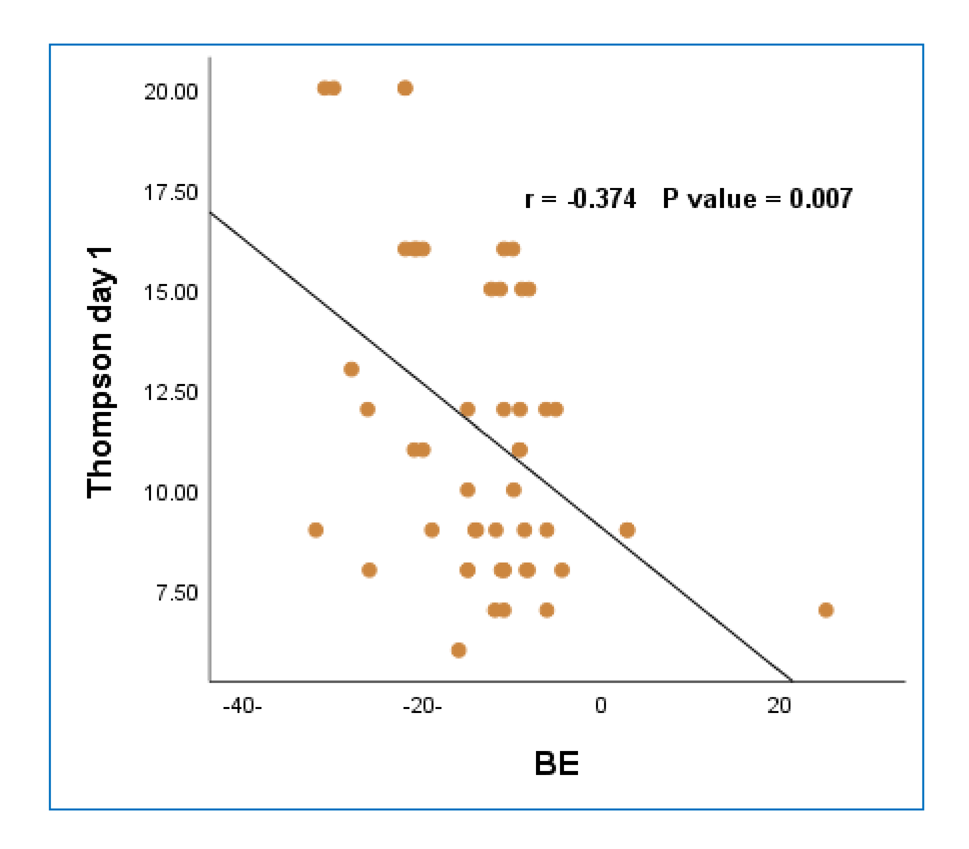
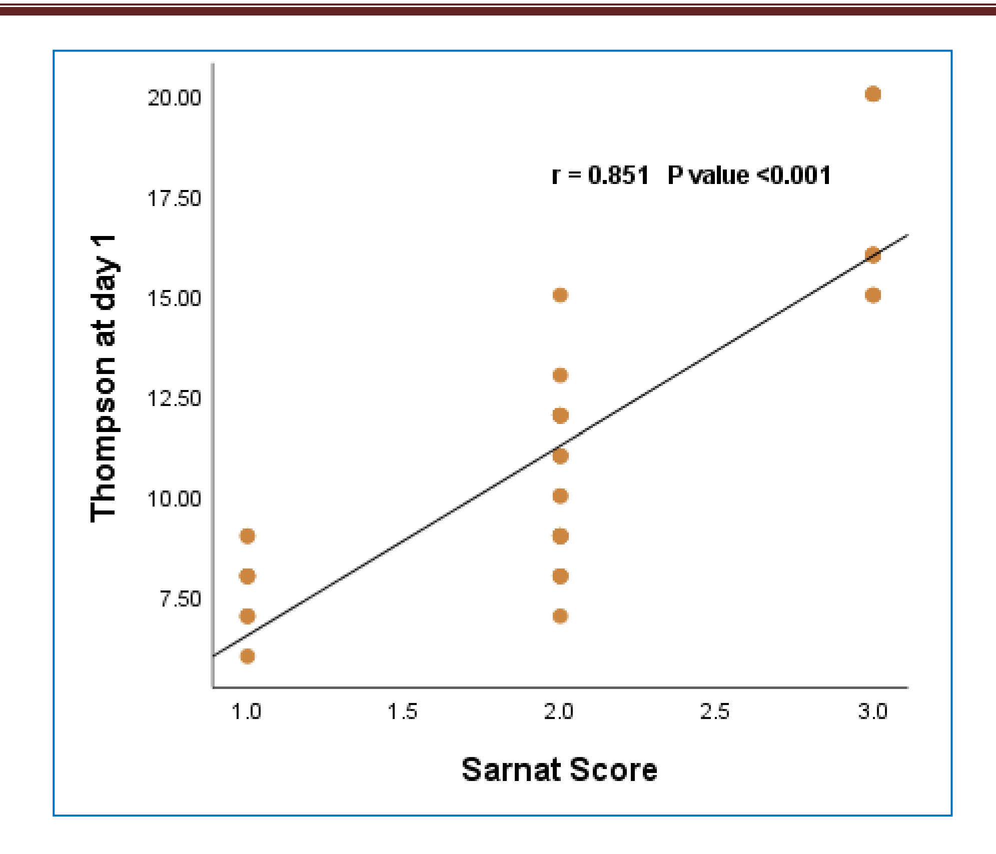


Figure (20):Correlation between Thompson score at D1 and Hco3



Figure(21):Correlation between Thompson score at D1 and BE



Figure(22):Correlation between Thompson score at D1 and Sarnat score

❖ **At day 1:**

- There were a negative correlation between Thompson score and the following:

✓Apgar 5min. (r = -0.321 & P value = 0.023),

✓PH (r = -0.324 & P value = 0.022),

✓HCO3 (r = -0.414 & P value = 0.003)

✓BE (r = -0.374 & P value = 0.007)

-There was positive correlation between thompson score and Sernat score:

✓Sarnat Score(r=0.851&P Value =<0.001)

-There were no significant correlation between Thompson score and hospital stay, maternal age, Apgar 1min. and PCO2. ***(Table(24)& Figures(18,19,20,21,22)***

Table (25):Correlation analysis between Thompson score at day 3 and other study parameters

Thompson Day 3		
Hospital stay	R	-0.14
	P value	0.342
Maternal age(years)	R	0.085
	P value	0.566
Apgar 1 min	R	0.028
	P value	0.849
Apgar 5 minutes	R	-0.079
	P value	0.596
PH	R	-0.11
	P value	0.456
PCo2(mm.Hg)	R	-0.041
	P value	0.783
HCo3(mEq/litre)	R	-0.25
	P value	0.086
BE(mmol/litre)	R	-0.262
	P value	0.072

BE = Base excess

At day 3

- There were no significant correlation between Thompson score and different study parameters. ***(Table(25))***

Table (26): Correlation analysis between Thompson score at day 7 and other study parameters

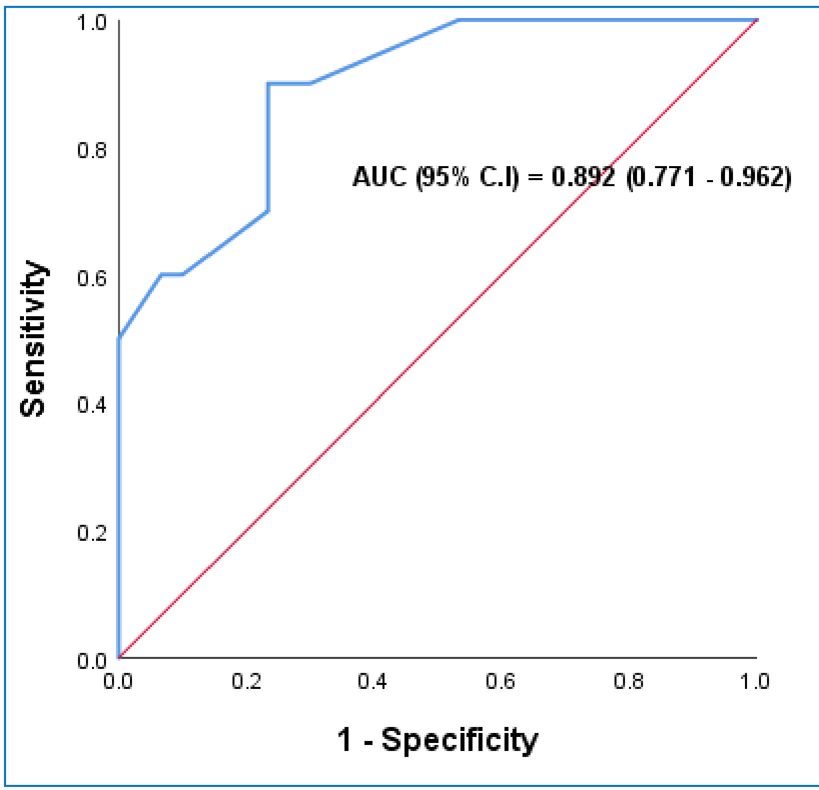
	Thompson Day 7	
Hospital stay	R	0.16
	P value	0.311
Maternal age	R	0.178
	P value	0.26
Apgar 1 min	R	-0.033
	P value	0.837
Apgar 5 minutes	R	-0.074
	P value	0.64
PH	R	-0.218
	P value	0.166
PCo2(mm.Hg)	R	-0.011
	P value	0.944
HCo3(mEq/litre)	R	-0.157
	P value	0.32
BE(mmol/litre)	R	-0.164
	P value	0.3

BE = Base excess

❖ At day 7:

- There were no significant correlation between Thompson score and different study parameters. ***(Table(26))***

➢ Mortality prediction



Figure(23):ROC analysis

Table (27): ROC analysis of Thompson score at day 1 for prediction of mortality

	AUC (95% CI)	SE	Best cutoff	Sensitivity	Specificity	P value
Thompson score at Day 1	0.903 (0.801 - 1.0)	0.043	10.0	90.0	76.7	<0.001

AUC = Area Under Curve 95%CI = 95% Confidence Interval SE= Standard Error

❖ ROC analysis of Thompson score at day 1 for prediction of mortality showed Area Under Curve (AUC) of 0.903 with 95% confidence interval ranging from 0.801 to 1.0. Best cutoff point for differentiation was 10 at which sensitivity and specificity were 90.0% and 76.7% respectively. This was statistically significant (P value <0.001). ***(Table(27) & Figure(23))***

➢ B. Multivariate logistic regression analysis

Table (28) Multivariate logistic regression analysis for prediction of mortality

	S.E.	Wald	OR	95% C.I. for OR	P value
Maternal age	0.214	7.232	1.778	1.169 - 2.704	0.007
Apgar 5 min	0.567	5.277	3.676	1.21 – 11.235	0.022
HCo_3	0.226	3.27	1.505	0.966 - 2.345	0.071
Thompson at Day 1	0.313	10.633	2.774	1.502 - 5.121	0.001

B = regression coefficient SE = Standard Error OR = Odds Ratio 95% CI = 95% Confidence Interval

- ❖ Stepwise logistic regression analysis was done for prediction of mortality. It revealed that predictors were:

✓Maternal age:

- ❖ For one year increase in maternal age, risk of mortality increase by 77% (OR = 1.77 – 95%CI = 1.169 – 2.704)

✓Apgar 5min:

- ❖ For one unit decrease in Apgar score, risk of mortality increases about 3.5 time (OR = 3.676 – 95%C.I = 1.21 – 11.235)

✓HCO3:

- ❖ For one unit increase in HCO3, risk of mortality increases 50% (OR = 1.505 – 95%C.I = 0.966 – 2.345)

✓Thompson at day 1:

- ❖ For one unit increase in Thompson score, risk of mortality increases about 3 times (OR = 2.774 – 95%C.I = 1.502 – 5.121). ***(Table(28))***

Discussion

Despite major advances in perinatal care in the past decades, asphyxia remains a severe condition leading to significant mortality and morbidity. The term “asphyxia” is derived from the Greek and means “stopping of the pulse”. Perinatal asphyxia is a condition characterized by an impairment of exchange of the respiratory gases (oxygen and carbon dioxide) resulting in hypoxemia and hypercapnia, accompanied by metabolic acidosis **(Bax, 2007)**

Hypoxemia may be defined as the “diminished amount of oxygen in the blood supply”, while cerebral ischemia is defined as the “diminished amount of blood perfusing the brain”. Cerebral ischemia is the more important of the two forms of oxygen deprivation because it also leads to glucose deprivation. The terms hypoxia-ischemia and asphyxia are often used interchangeably, but they are not equivalent from a pathophysiological view point **(Volpe, 2001).**

Four million newborn infants experience birth asphyxia each year, accounting for an estimated one million deaths and 42 million disability-adjusted life years . Many of these infants sustain significant brain injury and develop long-term sequelae, most commonly cerebral palsy, epilepsy, and sensory deficits **(Saugstad, 2011).**

Hypoxic Ischemic Encephalopathy (HIE) is the term commonly used to describe the neurological syndrome that occur following perinatal asphyxia **(Coovadia, 1998).** The pattern of risk factors, the nature of sequelae and the options and priorities for intervention (both preventive and therapeutic) are significantly different than in the industrialized countries **(Costello, 1994).** Until recently, there were no specific

strategies for prevention of brain injury in term and near-term infants. Neuroprotection with brain-specific therapies especially brain hypothermia is a promising therapy for neuroprotection for encephalopathy presumably due to hypoxic ischemia **(Shankaran et al., 2008).**

Several grading systems have been developed to assess neonatal encephalopathy in infants with perinatal asphyxia such as the post asphyxia score (PAS) (**Lipper et al., 1986) ,** the neonatal behavioural neurological assessment **(Bao et al., 1993) ,** the Sarnat and Sarnat grading system **(Sarnat, 1976)** and the Thompson score. The Thompson score is a simple clinical method of assessment of HIE in neonates with perinatal asphyxia, Derived from the Sarnat and Sarnat grading system **(Sarnat, 1976) .**

The Thompson score includes a neurological examination, assessment of respiration and fontanelle tension. The neurological components are tone, level of consciousness, the presence of fits, posture, the Moro reflex and the grasping and sucking reflex. The method is quick to perform, requires no additional training for medical or paramedical personal and requires no equipment. In the scoring system, a score of 0 is normal and the maximum score is 22 which signifies the worst possible status of HIE. Infants with score 1–10 are considered to have mild HIE, 11–14 have moderate HIE and 15–22 are considered to have severe HIE. In normothermic infants, a maximum score of > 10 during the first 7 days of life predicts an abnormal outcome **(Thompson et al., 1997).**

This study was done to assess the role of serial Thompson score at day 1, 3, 7 in predicting the early neonatal outcome in post asphyxiated term neonates.

Our study was a prospective cross sectional study, conducted on 50 full term neonates admitted in Neonatal Intensive Care Unit, Department of Pediatrics, Benha University Hospitals and Ahmed Maher Teaching Hospital with a provisional diagnosis of perinatal asphyxia from April 2018 to December 2018 .All patients were subjected to complete history taking, full clinical examination and laboratory investigations including CBC, CRP, cord blood gases, serum electrolytes, BUN, serum creatinine, liver function test, PT, PTT, INR, cranial U/S, Echo when indicated, Thompson score on day 1,3,7 of life, Sarnat staging and cases were followed up clinically and laboratory until discharge.

Demographic data of the patients were analyzed first and included gender, mode of delivery, body weight and gestational age of the cases.In our study, the mean gestational age was 38.32 weeks and the mean birth weight was 3.260 gm ± 0.625 . Gestational age of neonates did not appear to be significant risk factor in this study, as we excluded all preterm births less than 37 weeks and were only interested for the perinatal risk factors associated with birth asphyxia in term neonates. Males were predominant among cases represent 56% of neonates while 44% were females.

Birth weight in relation to the incidence of HIE was mentioned in several studies**. (Badawi et al., 1998)** found that growth restriction was the strongest risk factor for neonatal encephalopathy in their study.There were no significant differences between survivor and non-survivor neonates as regard gender , this comes in agreement with the study of **(Girish et al., 2014)** in which asphyxiated neonates had similar male : female ratio, mean age, and mean birth weight. Similarly, the study done by **(Askenazi et al., 2012)** who observed no statistically significant differences in demographic variables.

As regard mode of delivery , 33(66%) were delivered by LSCS which in some cases followed frequent trials of normal labor, compared to 17 (34%) were delivered vaginally and this in agreement with **(Cousen, 2005)** who found that asphyxiated neonates were delivered by LSCS rather than vaginal delivery. Different studies also describe this inverse association between elective cesarean section and birth asphyxia. In recent years, the rate of cesarean section had increased to a record level of 46% in China and to levels of 25% and above in many Asian, European and Latin American countries.The rate has increased significantly in the United States, to 33 percent of all births in 2011, up from 21 percent in 1996 **(Majeed et al., 2007).**

Higher maternal age seems to be significant risk factor for perinatal asphyxia. In our study , for one year increase in maternal age, risk of mortality increase for 77% (OR= 1.77-95% CI =1.169-2.704). Mean maternal age in non-survivors was 32 years. This was similar to the results reported from Sweden **(Milsom et al., 2002).**

Maternal risk factor was seen in 34 (68%) cases which was higher than **(Dongol et al., 2010)** (37.2%) and **(DaliP et al., 2016)** and this may be due to poor antenatal care and poor facilities delivered by health care unites in remote areas, and the same as **(Shrestha et al., 2009)** (65%) . In our study ,obstructed labour was major risk factor for HIE and was observed in 11(22%) of cases due to instrumental delivery, followed by gestational diabetis 5 (10%), followed by ruputure uterus in only 8% of cases although all cases whose mother had rupure uterus were died. This is in contrast with **(synder and Coherty, 2004)** who found maternal diabetis was the most common risk factors and the study made by **(Majeed et al., 2007)** who found anemia was the most frequent factor

(60%) as it lead to intrapartum hypoxia while in our study maternal anemia was observed in 2 cases only.

While efforts are made in improving the health-care system by making available basic health services, the Apgar scoring should remain a guide in determining the physiologic state of the newborn at birth and also monitoring the effectiveness of resuscitation. The mean Apgar score at 1 minute and 5 minute was 3 and 5 respectively. This was statistical significant (P value <0.001) and agrees with **(Karlsson et al., 2010)** who noticed that the first and fifth min. Apgar scores of neonates with HIE in their study were significantly lower than those Apgar scores of the control group.

An integral criterion of the ACOG guideline for perinatal asphyxia is an umbilical cord arterial blood sample obtained at delivery showing a pH less than 7 and a base deficit of 12 mmol/L or more **(ACOG, 2003).** However, **(Robertson, 2002)** stated that scalp and/or umbilical artery pH levels of less than 7.2 in the presence of clinical signs could be suggestive of HIE. In our study , we found that the mean pH was 7.12 ±0.24 and mean bicarbonate was 14.1 ±4.2.

ABG was done to all neonates , there was highly statistical significanct decrease in both Ph , HCO3 and base deficit (negative correlation with thompson score at day 1) while there was no statistical significance regarding PCO2, because the levels of PaCO2 and PaO2 fluctuate rapidly and dramatically, and can only reflect a transient condition at sampling. On the contrary, pH and BE reflect the outcomes of hypoxia and are more stable, this comes in agreement with **(Herrera, 2011) .**

In our study , mild Thompson score on day 1,3,7 was 25 (50%) , 31(62%), 32(64%) respectively , moderate Thompson score on day 1,3,7 was 11(22%) ,11(22%), 8(16%) respectively and severe Thompson score on day 1,3,7 was 14(28%),6(12%), 2(4%), There was clinical improvement among HIE patients as indicated by serial Thompson score done on day 1, 3 and 7. This agrees with **(DaliP et al., 2016)** who concluded that mild Thompson score on day 1, 2, 3 was 96 (66.2%), 119 (82.06%), 125 (86.20%), moderate Thompson score on day 1,3, 7 was 13 (8.9%), 6 (4.13%), 2 (1.37%) and severe Thompson score on day 1, 3, 7 was 36 (24.8%), 13 (8.96%), 7 (4.82%) respectively.

Neonatal seizures are considered a hallmark in the diagnosis of HIE. 24 (48%) of patient develop seizures in our study, 41% of cases experienced subtle convulsion in the form of smacking , suckling, blincking while 29% experienced tonic convulsion, 29% of cases had multifocal convulsion. This is slightly higher than **(Sekela et al., 2009)** where (41.7%) develop seizures and found that Neonates who scored >10 had a risk of developing convulsions. The risk of having convulsions was 3 times higher among infants with moderate HIE relative to those with mild HIE and this agreed with our study in which, majority of patients were stage 2 (62%), as regard Sarnat staging . Only (37%) of stage 3 had seizures , it could be due to the over sedation of high-risk neonates.

Most infants with significant birth asphyxia have injury to the lungs and many require mechanical ventilation. Respiratory complication was the most common organ dysfunction (68%) in our study in the form of respirator distress require mechanical ventilation and PPHN, followed by renal dysfunction (defined by increase in serum creatinine > 1 to 1.5 mg/dl) (48%), then hepatic dysfunction (defined by ALT > 50 U/L and

AST > 150 U/L).This agrees with **(Higgins et al., 2006)** who carried out a retrospective study on 130 term neonates with perinatal asphyxia, they found that pulmonary dysfunction was the commonest to occur (86%) followed by hepatic dysfunction in (85%) of cases, then renal dysfunction in (70%) of cases.

On the other hand, our results disagrees with **(TEKIN, 2003)** who found renal dysfunction was the commonest to occur followed by pulmonary dysfunction.

48% of our cases had renal impairment this was higher than the incidence reported in the study of **(Khan et al., 2014)** in which (44%) of the studied newborn with birth asphyxia had renal impairment, While another studies that were done by **(Girish et al., 2014)** and **(Sarafidis et al., 2012)** as the incidence was (64%) and (61.5%) respectively. Since the definition of AKI is not very refined in the newborn period, the assessment of biomarkers of kidney injury are often sub-optimal. Serum creatinine will not begin to rise until 25 to 50% of renal function is lost, thus significant injury can occur without changes in creatinine **(Askenazi et al., 2009).**

In our study, only 23 patient performed ECHO, of them only 16 (32%) affected in the form of PPHN , functional tricuspid regurge (14 cases) and decrease myocardial contractility (2 cases). This agree with **(Satyan, 2018)** who found that 22% of his cases had pulmonary hypertension. It has been well documented that exposure to chronic hypoxia cause vasoconstriction of pulmonary vessels. Asphyxia may cause myocardial ischemia, which usually is transient, but result in cardiogenic shock and death **(Levene and De Vries, 2010).**

MRI is the optimal technique to detect perinatally acquired cerebral lesions However, it is expensive and often requires sedation and transportation of the neonate and therefore is many times not practical. In our study , it was done only in 3 patients, Two of them showed brain affection (in the form of abnormal signals of posterior limb of internl capsule in T1, abnormality of basal ganglion). Cranial Ultrasound and Doppler on the other hand are cheaper, can be done at the bedside and with proper technique are quite sensitive for detection of brain injury. In this study 52 % of patients showed signs suggestive of HIE on cranial U/S while 48% showed no evident sonographic signs. Early US findings of HIE include a global increase in cerebral echogenicity and obliteration of the cerebrospinal fluid (CSF) containing spaces, suggesting diffuse cerebral edema which was found in 9 cases of our study . Increased echogenicity in the basal ganglia, thalami, and brainstem can also be seen in the first week but is more readily apparent after 7 days **(Huang and Castillo, 2008),** in our study it was evident in 2 cases.

Color Doppler imaging is used to screen the vasculature for patency and resistance to flow. **(Baytur et al., 2004)** found that normally cerebral arterial blood velocity decreases immediately within the first few hours after birth and increases within 24 hours as part of neonatal adaptation. Decreased RI is noted to be an abnormal finding and is postulated to be caused by impairment in cerebral autoregulation and subsequent decreased cerebrovascular resistence and increase in end-diastolic flow. Normal values of resistive indices according to their study were found to be around 0.70 ± 0.05 in ACA and MCA in the first 24 hours after birth. This correlates well with our findings in which there is 15 cases had low RI < .7.

Total of 50 neonate, 20 (40%) died and 8 (16%) exhibit morbidity in the form any neurological examination abnormality including hypotonia poor suckling (discharged on ryle feeding) , infants have seizures require anticonvulsants drugs on discharge ,any radiological abnormalities . This is higher than **(Sharada, 2006)** who found that 20-25% died within the newborn period and up to 25% of the survivors will exhibit retardation, cerebral palsy and epilepsy and this is because of increase number of cases who were moderate and sever asphyxiated, and lack of facilities for close monitoring in the neonatal unit and prevelance of sepsis as 6 cases died in our study due to sepsis and septic shock and complication of M.V as 2 cases died from bilateral Tension pneumothorax , this raises attention to importance of training of NICU team of infection control measures and lung protective mechanical ventilation stratigies. Long term neurodevelopmental outcome was not assessed in our study and outcome prediction could better be assessed with the help of neuroimaging.

12 (92.3%) cases of severe HIE were died and only one case (7.6%) survived with abnormal outcome while in moderate HIE 40% died and 60% survived. This agrees with **(Thornberg et al., 1995)** who studied 227 infant in retrospective study and found infants with severe HIE either died or developed neurological damage. Half of the infants with moderate and all infants with mild HIE were reported to be normal.

In our study, we found that the HIE score was highly specific in detecting early neonatal mortality (within 7 days of life) among neonates who had moderate and severe HIE as median Thompson score in non-survivors in day 1, 3, 7 was 16, 13, 11 respactively. The risk of dying during the neonatal period increased with increasing HIE score. There was a good correlation between the Thompson score at day 1 and death as Median Thompson score was higher in non-survivors (16) than that of

survivors (9), this agrees with **(Therese et al., 2013)** (r = 0.42 & P value= 0.0024).

There is also positive coreelation between Thompson sscore at day1 and Sarnat stage (r = 0.851 & P value < 0.001) , this agrees with **(Therese et al., 2013)** (r = 0.77 & P value < 0.0001).

In normothermic infants, Thompson score of >10 at day 1 of life predicts an abnormal outcome with 90% sensitivity and 76.7% specificity. This agrees with **(DaliP et al., 2016)** which predicts an abnormal outcome with 100% sensitivity and 61% specificity unlike**(Thorsen et al., 2016)** who predict Thompson score >12 for abnormal outcome.

Summary and Conclusion

Perinatal asphyxia is a lack of blood flow or gas exchange to or from the fetus in the period immediately before, during or after the birth process. Perinatal asphyxia can result in profound systemic and neurologic sequelae due to decreased blood flow and/or oxygen to a fetus or infant during the peripartum period. When placental (prenatal) or pulmonary (immediate post-natal) gas exchange is compromised or ceases altogether, there is partial (hypoxia) or complete (anoxia) lack of oxygen to the vital organs. This results in progressive hypoxemia and hypercapnia. Anaerobic glycolysis and lactic acidosis will result. Neonatal hypoxic-ischemic encephalopathy refers specifically to the neurologic sequelae of perinatal asphyxia.

Throughout the world each year, an estimated 20% of the 4 million neonatal deaths and 8% of all deaths in < 5 years of age are associated with signs of asphyxia at birth. Thompson score is a clinical tool comprising of a set of clinical signs associated with central nervous system (CNS) dysfunction. It is used to assess status of a child following birth asphyxia. The score consists of a clinical assessment of nine signs (Tone, Level of consciousness, Fits, Position, Primitive reflexes, Respiration, Fontanel tension). Each sign is scored from 0 to 3 and the score for each day is totalled. The higher the score the more severely affected the infant. Score 0 is considered normal. The maximum possible score on any one day is 22. Infants with score (1–10) are considered to have mild HIE, (11–14) have moderate HIE and (15–22) are considered to have severe HIE

Our study was conducted on 50 full term neonates admitted in Neonatal Intensive Care Unit, department of Pediatrics, Benha University

Hospitals and Ahmed Maher Teaching Hospital from April 2018 to December 2018 with a provisional diagnosis of perinatal asphyxia. All patients were subjected to complete history taking, full clinical examination and laboratory investigations including CBC, CRP, blood gases, serum electrolytes, BUN, serum creatinine, liver function test, blood gases, PT, PTT, INR, cranial U/S, chest x-ray, Thompson score on day 1,3,7 of life, Sarnat staging . ECHO ,MRI, CT brain was done when indicated. Cases were followed up clinically and laboratory.

The results of our study revealed the following:

- 56% of neonates were males. 44% were females. The most frequent mode of delivery was Cesarean section (66.0%). Vaginal delivery represented 34%.
- The mean gestational age was 38.32 wks and median birth weight 3.260 gm.
- In our study ,obstructed labour was observed in 11(22%) of cases followed by gestational diabetis 5(10%) then rupture uterus and pre-eclampsia.
- Median Apgar score at 1 minutes was (3) and at 5 minute (5).
- Mean PH was 7.12 with standard deviation ± 0.24.
- Seizures was experienced in 48% of patients. Subtle convulsion was the most common.
- In our study , mild Thompson score on day 1,3,7 was 25 (50%) , 31(62%), 32(64%) respectively , moderate Thompson score on day 1,

3, 7 was 11(22%) ,11(22%), 8(16%) respectively and severe Thompson score on day 1,3,7 was 14(28%),6(12%), 2(4%).

- Serial improvement of median of serial Thompson score.
- Regarding multiorgan affection , respiratory dysfunction represent 68% of cases followed by renal affection ,then hepatic dysfunction and last coagulopathy.
- Cranial U/S affection was found in 52% of cases.
- 40% of our cases died, while 16% shows morbidity and 44% were discharged normal.
- There were no significant differences between survivor and non-survivor neonates as regard gender and mode of delivery .
- Our study shows that Rupture uterus was higher (20.0%) in non-survivors than that in survivors.
- Median Apgar score at 5 minutes was higher in survivors (6) than non-survivors (4).
- Our study shows that Respiratory complication 100% ,renal affection 70% and Coagulopathy 70% was higher in non-survivors that that of survivors.
- Median Thompson score was higher in non-survivors (16) than that of survivors (9).
- There were a negative correlation between Thompson score and PH Apgar at 5 minute and HCO3.

- There was positive correlation between thompson score and Sarnat score.
- The HIE scoring system used in this study is highly predictive of neonatal outcome . ROC analysis of Thompson score at day 1 for prediction of mortality showed Area Under Curve (AUC) of 0.903 with 95% confidence interval ranging from 0.801 to 1.0. Best cutoff point for differentiation was 10 at which sensitivity and specificity were 90.0% and 76.7% respectively. This was statistically significant (P value <0.001).
- Thompson score allows a very precise description of infants by assigning a numeric score rather than ‘mild’, ‘moderate’ or ‘severe. and there is no requirement of Electroencephalogram which is beneficial in resource limited countries like ours.

Recommendations

- The Thompson score should be used for all infants with birth asphyxia at first day so as to enable the clinician to identify infants that may be at high risk of neurodevelopmental abnormality.

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الملخص العربي

يعرَّف الاختناق الوليدي بانه نقص في تدفق الدم أو تبادل الغازات إلى الجنين أو منه في الفترة التي تسبق عملية الولادة مباشرة أو أثناءها أو بعدها. يمكن أن يؤدي الاختناق الوليدي إلى مضاعفات جسمانية وعصبية عميقة بسبب انخفاض تدفق الدم و / أو الأكسجين إلى الجنين أو الرضيع خلال الفترة المحيطة بالولادة. عندما تتعرض عملية تبادل الغازات في المشيمة (ما قبل الولادة) أو الرئة (مباشرة بعد الولادة) للخطر أو تتوقف تمامًا ،ذلك يؤدي الي نقص جزئي (نقص الأكسجة) أو نقص كامل في الأكسجين للأعضاء الحيوية. هذا ينتج عنه نقص الأكسجين التدريجي وزيادة ثاني اكسيد الكربون. وينتج عنه ايضا التحلل اللاهوائي وزيادة حمض اللاكتيك في الدم . يشير اعتلال الدماغ الدماغي الإقفاري الوليدي تحديدًا إلى اعتلال الجهاز العصبي الناتج عن الاختناق الوليدي.

في جميع أنحاء العالم كل عام ، تشير التقديرات إلى أن ٢٠٪ من حالات وفيات الأطفال حديثي الولادة البالغة ٤ ملايين وفاة و ٨% من نسبة الوفيات في الاطفال اقل من ٥ سنوات ترتبط بعلامات الاختناق عند الولادة.

ان تصنيف طومسون أداة إكلينيكية تشتمل على مجموعة من العلامات السريرية المرتبطة بخلل الجهاز العصبي المركزي يتم استخدامه لتقييم حالة الطفل بعد اختناق الولادة. تصنيف طومسون هو اداة تقييم اكلينيكية سريرية تصف قوة العضلات و مستوي الوعي , حدوث تشنجات , وضعية الجسم , منعكس مورو , قوة الامساك , قوة المص , التنفس , فتحة النافوخ . يتم تسجيل كل علامة من ٠ إلى ٣ ويتم احتساب مجموع النقاط لكل يوم. وكلما ارتفعت درجة أثرت بشدة على الرضيع. النتيجة صفر تعتبر طبيعية. أقصى درجة ممكنة في أي يوم هي ٢٢. يعتبر الرضع ذوو النقاط (١-١٠) لديهم اعتلال دماغي بسيط , والرضع ذو النقاط (١١-١٤) لديهم اعتلال دماغي متوسط , والرضع ذو النقاط (١٥- ٢٢) لديهم اعتلال دماغي شديد .

قد أجريت دراستنا على ٥٠ طفل مكتملي النمو في قسم الاطفال وحدة العناية المركزة الخاصة بحديثي الولادة في مستشفيات بنها الجامعية ومستشفي احمد ماهر التعليمي في الفترة من ديسمبر ٢٠١٨ الي ابريل ٢٠١٩ وتم تشخيصهم مبدئيا بالاختناق الوليدي.

تم اخضاع جميع المرضي لاخذ التاريخ المرضي كاملا , فحص اكلينيكي شامل , فحوصات معملية وتشمل صورة دم كاملة , بروتين سي التفاعلي , وظائف كبد , وظائف كلي

,سيولة الدم, غازات دم من الحبل السري , اشعة تليفزيونية علي المخ و اشعة عادية علي الصدر وتصنيف سارنات وتم تطبيق تصنيف طومسون في اليوم الاول والثالث والسابع من الولادة. تم عمل موجات صوتية علي القلب واشعة رنين مغناطيسي علي المخ واشعة مقطعية علي المخ اذا استدعت الحالة ذلك. تم متابعة الحالات اكلينيكيا ومعمليا.

وقد اظهرت نتائجنا مايلي:

- ٥٦% من المواليد ذكورا , بينما ٤٤% من المواليد اناثا , كانت الولادة القيصرية هي الاكثر شيوعا بنسبة ٦٦% , بينما تمثلت الولادة الطبيعية في ٣٤% .

- كان متوسط عمر الحمل ٣٨,٣٢ أسبوعًا ، ووزن الولادة المتوسط ٣,٢٦٠ جم.

- عوامل الخطورة في دراستنا تشمل الولادة المتعثرة في ١١ (٢٢%) من الحالات يليها سكر الحمل في ٥ (١٠%) من الحالات , ثم تسمم الحمل.

- كان متوسط تقييم ابجر عند الدقيقة الاولي ٣ والدقيقة الخامسة ٥ .

- • متوسط حموضة الدم كان ٧,١٢ مع انحراف معياري ± ٠,٢٤.

- وجود تشنجات في ٤٨ % من الحالات . كان التشنج الخفي هو الاكثر شيوعا .

- كان تصنيف طومسون بسيط في اليوم الاول والثالث والسابع بنسبة ٢٥ (٥٠ ٪), ٣١ (٦٢ ٪) ، ٣٢ (٦٤ ٪) على التوالي. وكان تصنيف طومسون متوسطا في اليوم الاول والثالث والسابع بنسبة ١١ (٢٢ ٪) ، ١١ (٢٢ ٪) ، ٨ (١٦ ٪) على التوالي , وكان تصنيف طومسون حاد في اليوم الاول والثالث والسابع بنسبة ١٤ (٢٨ ٪) ، ٦ (١٢ ٪) ، ٢ (٤ ٪).

• التحسن التسلسلي لمتوسط درجة طومسون .

- فيما يتعلق باعتلال الاعضاء التعددي, يمثل فشل الجهاز التنفسي ٦٨% من الحالات ,يليه اعتلال وظائف الكلي يليه اعتلال كبدي ثم اخيرا اعتلال تخثر الدم.

- بالنسبة للاشعة التليفزيونية علي المخ , تبين وجود اعتلال في ٥٢% من الحالات .

- توفي ٤٠ ٪ من الحالات لدينا ، في حين أن ١٦ ٪ قد اظهروا اعتلالا و ٤٤ ٪ خرجوا بشكل طبيعي.
- لم تكن هناك فروق ذات دلالة إحصائية بين الناجين والمواليد غير الناجين فيما يتعلق بالجنس ونوع الولادة.
- أظهرت دراستنا أن انفجار الرحم كان أعلى (٢٠,٠٪) لدى غير الناجين منه في الناجين.
- كان متوسط تصنيف أبجر في ٥ دقائق أعلى في الناجين (٦) من غير الناجين (٤).
- أظهرت دراستنا أن المضاعفات الجهاز التنفسي بنسبة ١٠٠ ٪ ، والاعتلال الكلوي ٧٠ ٪ ، وتجلط الدم ٧٠ ٪ كانت أعلى في غير الناجين من الناجين.
- كان متوسط تصنيف طومسون اعلي في غير الناجين ١٦ عن الناجين ٩.
- توجد علاقة عكسية بين تصنيف طومسون ونسبة حموضة الدم ونسبة البيكربونات في الدم.وتصنيف ابجر عند ٥ دقائق.
- هناك علاقة طردية بين تصنيف طومسون وتصنيف سرنات.
- اظهر منحني الخاصية العملياتية الخاص بمقدرة تصنيف طومسون للتنبوء بالوفيات في اليوم الاول , ان المساحة تحت المنحني ٠,٩٠٣ مع فاصل ثقة ٩٥% يتراوح بين٠,٨٠١ الي ١ وكانت افضل نقطة قطع للتمايز هي ١٠ حيث كانت الحساسية والنوعية ٩٠% و ٧٦,٧% علي التوالي وكان هذا ذو دلالة احصائية .
- يقدم تصنيف طومسون وصفًا دقيقًا جدًا للأطفال الرضع من خلال تعيين درجة رقمية بدلاً من "خفيفة" أو "معتدلة" أو "شديدة". وليس هناك أي حاجة الي تخطيط كهربي للدماغ وهو مفيد في البلدان المحدودة الموارد مثل بلدنا.